First Edition: 2026

HIV CUREiculum

Participants Guide



African Alliance
Altahaluf al'Afriqiu
التحالف الأفريقي

AHCC
AFRICA HIV CURE CONSORTIUM

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Contributors

This resource has been compiled by the African Alliance, in partnership with the members of the African HIV Cure Consortium and with financial support from the University of Georgetown, ViiV Healthcare, Gates Foundation and Aidsfonds.

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Early iterations of the HIV CUREiculum were reviewed by the Technical Working Group of the African HIV Cure Consortium (AHCC). The following AHCC member organisations contributed to its development and review:

- Centre for Infectious Diseases Research in Zambia
- Sub-Saharan Network for TB/HIV Research Excellence
- AVAC
- HIV Cure Africa Acceleration Partnership

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Dedication

A DEDICATION TO PARENTS, CHILDREN, NEIGHBOURS, RELATIVES, LOVERS, COMRADES, FRIENDS, LEADERS AND FOLLOWERS LIVING WITH HIV

Stranger in the Mirror of My Life

by Senator Ihenyen,[1] Nigerian Poet and Author

Before me is a mirror
A mirror beside my bed
Away from the sun burning brightly
Outside the window's blinds in my darksome room

For a moment
Before the mirror
I stand to see the face of the victim
Whose result returned a death sentence
After a test
And another test and yet another
But they kept coming back
One and the same
Like the torrent of tears that keep returning to your eyes
When the heart remains wet with worries

Wavering worries of one's life walking away from the door,
As the wall clock ticks unrestrained,
Untouched, unconcerned,
Like the footsteps of the world around you moving on,
Unaffected, unmoved, unstirred.
I know this face hiding in the mirror isn't me –
It couldn't be me!
I look straight into her eyes,
It was then she looked back at me –

Petrified, she crept back into the closet of her life.
I walk slowly and gently towards her,
Suddenly the stranger steps closer and closer towards me.
And when my feet froze on the floor
Upon the freezing fear that gripped me,
The stranger in the mirror startles –
Faint-hearted, intimidated

This stranger is not me
No, not me!
She is just a shadow –
The shadow of someone too locked-up in her closet to open up to me.
She is a stranger too steeped in shame to stand up to herself
And say:

"I'm Hannah,
I'm HIV positive –
How beautiful life could be
When I open the window's blinds in my heart
And let the rays of the sun
Overshadow the stranger in the mirror of my life."



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1. https://senatorihenyen.wordpress.com/3296-2/

Foreword

The CUREiculum: A Pan-African Call to Reclaim HIV Cure Science

The pursuit of an HIV cure is not merely a scientific endeavour; it is a political, cultural and moral imperative rooted in Africa's collective struggle for justice. From the vibrant townships of Soweto to the resilient communities of Kampala and the thriving networks of Kigali, African peoples have borne the heaviest burdens of the HIV pandemic, while being systematically marginalised from the centres of research, policy, and resource allocation. This is no accident. It is the legacy of colonial extraction and global health inequity.

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The CUREiculum challenges this legacy. It is **"a bold, Pan-African intervention and a tool designed to dismantle exclusionary systems and centre African voices, wisdom, and sovereignty in the global pursuit of an HIV cure".** While global progress in managing HIV through antiretroviral therapy (ART) has been significant, the ultimate goal remains a durable, functional cure. This goal is inseparably tied to Africa, which bears more than two-thirds of the global HIV burden. Yet from 1995 to 2024, only 0.02% of HIV cure-related publications listed an African institution[2] in first or last author positions, a stark indicator of structural exclusion.

2. https://pubmed.ncbi.nlm.nih.gov/40861434/

Groundbreaking Clinical and Foundational Research

A new era of African-led science is emerging, marked by landmark studies such as the HIV cure trial led by Professor Thumbi Ndung'u at the Africa Health Research Institute (AHRI) in Durban, South Africa. This trial[3], the first of its kind on the continent, gave participants ART within hours of infection. Once the ARVs had stopped the virus from replicating, participants were given powerful immune boosters. This combination treatment achieved promising results: 20% of participants remained off ART and virally suppressed for an average of 1.5 years after the trial's conclusion.

The next step is for scientists to figure out exactly how and why the treatment worked so well for this group. This study's significance lies not only in the science, but also in its ethics and the fact that the AHRI team intentionally enrolled 20 women, a population disproportionately affected by HIV but historically underrepresented in research. Ndung'u's trial is also significant because it proves that complex HIV cure research can be successfully conducted in resource-limited settings where the need is greatest.

Beyond clinical trials, foundational discoveries are also being driven by African scientists. Dr. Godfrey Dzhivhuho, a South African-born virologist, has investigated the role of the HIV protein called 'Rev' in helping the virus hide in the body even if the person has been on treatment for years. This is called 'viral latency'. What Dzhivhuho's work does[4] is help to explain why HIV can keep coming back when a person stops taking ART, and why some cure strategies (such as 'shock and kill') fail to achieve desired outcomes.

Strengthening Networks and Addressing Barriers

This rise in scientific leadership is supported by collaborative networks such as the Sub-Saharan African Network for TB/HIV Research Excellence (SANTHE), which works to build "intellectual and financial independence" among African researchers.

Their model, grounded in equitable partnerships and local ownership, stands in direct contrast to the extractive research norms of the past. Yet structural challenges persist. Many African researchers are locked out of high-impact journals due to unaffordable article processing charges. Others are consistently relegated to 'middle author' roles in international collaborations, limiting their recognition and career mobility.

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A Curriculum for Liberation

The CUREiculum is a clarion call for African unity and self-determination. Rooted in Pan-African values of solidarity, dignity and collective progress, this curriculum equips communities across the continent to engage with HIV Cure science on their own terms.

It bridges the technical complexities of virology with the urgent imperatives of health justice, providing advocates, researchers and communities with the language and frameworks needed to shape the future of science itself. This is not a simplified guide. It is a rigorous, politically conscious manifesto affirming Africa's rightful place at the forefront of global health innovation.



3. https://www.ahri.org/groundbreaking-south-african-hiv-cure-trial-shows-promising-results/
4. https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1012885

Reclaiming Africa's Scientific Legacy

Too often, Africa's contributions to knowledge have been erased or undervalued, from the ancient libraries of Timbuktu to today's innovations by scientists working under constrained conditions. Yet our continent has always been a crucible of resilience and ingenuity. The CUREiculum reclaims this legacy not as a plea for inclusion, but as a demand for ownership. "We are not guests in the house of science. We are its architects."

By centring African knowledge systems, community expertise and cultural wealth, this curriculum asserts our right to co-create the tools, systems and futures that ensure our survival and that we flourish.

A United Front for Health Justice

The CUREiculum is a vital instrument for transformation. It empowers advocates, health workers and policymakers to challenge the ethical blind spots of cure science and demand equitable access to its benefits. From the laboratories of Nairobi to the community clinics of Lusaka, we envision a continent where research serves the people, where data sovereignty is non-negotiable, and where scientific progress is measured by its impact on those most affected. This is a Pan-African vision that unites our 54 nations in a shared commitment to end HIV through collaboration, accountability and justice.

Breaking the Frame: From Capacity Imposed to Capacity Celebrated

For too long, Africa's engagement with global science has been framed through a paternalistic lens; one of 'capacity building', technical assistance and perpetual apprenticeship. This narrative casts African minds as incomplete, our institutions as inadequate, and our contributions as secondary.

We reject this frame entirely. The challenge before us is not a lack of capacity, but a failure to recognise it. African researchers, activists and community leaders have long sustained health systems, innovated under scarcity, and produced knowledge that global science often repackages without credit or compensation. The CUREiculum shatters this paradigm. It does not aim to 'build' capacity but to celebrate and amplify the brilliance already present across our continent. It demands that African institutions set the research agenda, that community wisdom shapes trial design, and that collaboration reflects mutual respect and not one-way extraction.

True cure readiness means Africa leads, defining how science is prioritised, governed and measured, from Accra to Addis Ababa, from Harare to Dakar.

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A Decolonial Path to an HIV Cure

The path to an HIV cure is not solely biomedical; it is profoundly decolonial. It cannot be forged by replicating systems that have historically excluded us from the laboratory and relegated us to the margins of global health. It must be built by the hands, hearts, and minds of African people; those with everything to gain and everything to contribute. The CUREiculum is a cornerstone in this movement: a tool to empower communities to demand justice, drive innovation, and shape a future where HIV is not only eradicated, but where the systems that sustained its inequities are transformed.

Let us, as one Africa, wield this curriculum with intention and power. Let us honour our shared history, celebrate our diverse strengths, and march towards a future where science serves the collective good of our continent.

The time for a Pan-African-led HIV cure is now.

A Message to Advocates

This Is Already Yours

To the advocates who have been trained, retrained, and trained again.
To those who have filled rooms, signed registers, completed workshops and carried toolkits.
To those who have been labelled 'beneficiaries' in one project and 'recipients' in the next.
To those whose brilliance has been framed as potential, not fact.

You have had your 'capacity built' for decades, often by people with less proximity, less insight, and less at stake than you.

You do not need to be given power.
You need to reclaim what has always been yours.

The knowledge you've built – through lived experience, political struggle and relentless advocacy – is not auxiliary to science. It is science. The data you collect, the questions you raise, the ethical challenges you pose; these are not 'community add-ons'. They are foundational to the future of HIV Cure.

And yet, you've been told to wait.
To participate only once protocols are finalised.
To advocate only within donor-approved frameworks.
To remain a sub-recipient, never a principal recipient.
To trust that inclusion is coming, if only you remain polite.

But the time for politeness has passed.
This is a moment for audacity.

The CUREiculum is not another training. It is a signal. A call. A set of tools designed not to shape you into someone else's definition of readiness, but to affirm that you are already ready.

Ready to take space in scientific discourse.
Ready to challenge exclusion in national strategic plans.
Ready to lead clinical engagement, demand ethical transparency, and hold governments and global actors accountable.

You do not need to ask for inclusion. You are already included, by the work you've done, the lives you've saved, and the truths you've spoken.

What remains is to seize the infrastructure, shape the narrative, and demand that the cure be delivered – not as a gift, but as a right; on your terms, in your language, for your people.

Because readiness is not something handed down from a podium.
It is something you carry every time you walk into a room, knowing exactly what justice looks like.

And it looks like you.

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PART 1

Introduction

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Introduction to this Guide

The CUREiculum was created to help communities affected by the burden of HIV understand and lead the push toward an HIV Cure.

The guide is grounded in the belief that African people, especially those living with HIV, should guide this work and shape the decisions that affect their health and future.

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The Africa HIV Cure Consortium (AHCC), led by the African Alliance, developed the CUREiculum together with community members, clinical experts and organisations who have been advocating for an HIV Cure for more than 20 years.

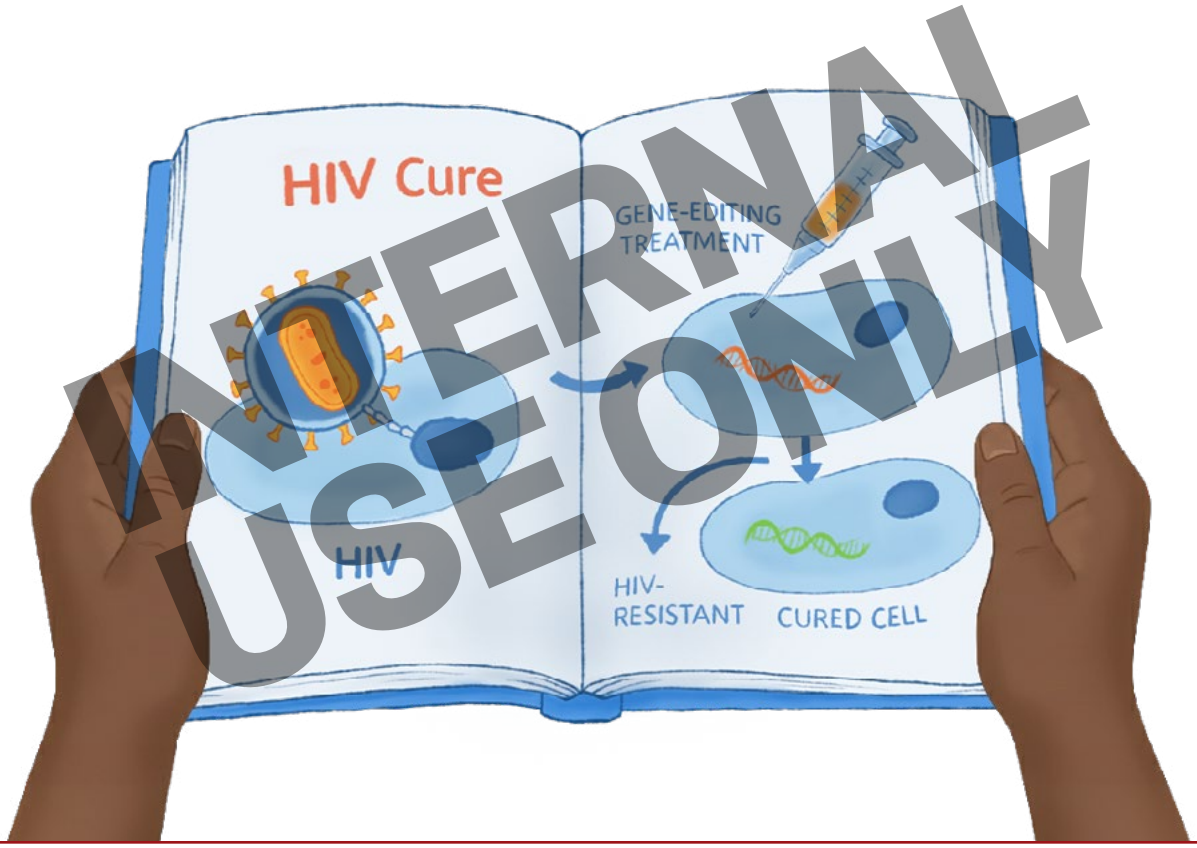
Their shared experience and leadership make this training a strong foundation for everyone joining the journey towards an HIV Cure.

Why a CUREiculum now?

While there is significant coverage of Anti-retroviral Therapy (ART), and many African countries are singularly focused on the 95-95-95 targets from UNAIDS, African civil society remains committed to pursuing an HIV Cure.

We acknowledge that sustained and wall-to-wall access to Pre-exposure Prophylaxis (PrEP) and Anti-retroviral therapy/ treatment (ART) cannot be guaranteed or assured. Therefore, HIV must be eliminated as a public health threat.

Even though ART has helped millions of people, many still struggle to get these medications because of barriers in the health system, stock-outs, stigma and fears about long-term drug resistance. While PrEP is a great way to stop HIV before it starts, many people still struggle to get it, stay on it, or know how well it works over time. Because of this, the promise of PrEP to help communities end HIV may not be fully realised.



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After more than 20 years of promoting treatment and prevention, we now know that the available strategies to control the HIV epidemic cannot do so by themselves. Because of this, scientists and public health leaders are again looking to an HIV Cure as a vital part of finally controlling the epidemic.

Over the past ten years, researchers working on an HIV Cure have made impressive progress. New tools – such as special antibodies, gene- and immune-based treatments, and mRNA technology similar to that used in COVID-19 vaccines – are giving real hope that several HIV Cure options could start to appear before 2030.

For many communities, the science behind HIV Cure research can seem complicated and hard to follow. This is why the CUREiculum was created: to make the information clear, accessible, and grounded in the lived experience of people living with HIV (PLHIV).

Built on more than 35 years of human rights advocacy, the CUREiculum honours the strength and leadership of PLHIV, who continue to lead the fight against HIV and the social challenges linked to it. The CUREiculum aims to support communities to understand, participate in and shape the journey towards an HIV Cure.

What is the purpose of this Guide?

Without thoughtful planning, training can be clumsy and not achieve its objective. This guide provides simple tools to help partners plan and roll out the CUREiculum so everyone is ready and aligned.

This guide also highlights who should be involved so that the training is community-led and credible:

- People living with HIV in the community
- Community-based partners hosting the training
- Advocates and interested community members who have a stake in an HIV Cure
- Partner representatives and country leads
- A small coordination group or steering team

By following this process, community advocates can strengthen their leadership, organise effective training, and play an active role in shaping the path towards a community-led HIV Cure.

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Implementation Roadmap: The CUREiculum

01. The Golden Rule of Delivery

Delivering without preparation can have unintended consequences for participants, resulting in ethical concerns. Thoughtful planning is a foundational requirement.

02. Planning Workshop

Target Duration
3 to 5 Hours

Used for training inception. Concludes successfully only when **all preparation documents** are completed.

Action Checklist

- ☑ Review Skeleton Agenda
- ☑ Include 5 Training Role-Players
- ☑ Nominate Coordination Cluster

03. The Partnership Compact

African Alliance
Strategic lead and curriculum stewards.

Host-Country NGO
CSOs ensuring local community participants.

Subject Partners
MoH, AHCC, or Global Fund stakeholders.

04. Governance Structure

Nominated Coordination Cluster:

- African Alliance Lead
- Partner Representative
- Host Assistant

Technical Oversight

"Occasional guidance as availability allows from the AHCC Technical Working Group for the HIV CUREiculum."

Our Approach to Learning

The African Alliance's work centres people's lived experiences, local knowledge and awareness of power dynamics. This means the CUREiculum is designed with PLHIV at the centre – your history, context, and expertise matter just as much as the scientific content.

Learning is not only about information; it is also about how we learn together.

The CUREiculum was created using a hands-on, discussion-based approach in which participants helped shape and improve each module.

A designer and the training team reviewed the visuals, stories and explanations to make sure they made sense and supported learning. Community feedback guided changes to language, images and teaching methods, all grounded in proven participatory and socio-behavioural practices.

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The AA CUREiculum: A Social Epistemology of Learning

We defer to lived experience, context, and patterns of power

01. Our Four Pillars of Knowledge

Participant Centered
The individual is at the heart of the process.

Indigenous Knowledge
Celebrating local wisdom and traditional insights.

Historical Legacies
Recognising the past to navigate the future.

Shared Perspectives
Amplifying the power of collective voices.

02. The Pedagogy

Content + Process = **Deep Knowledge**



- **Participants-as-Experts**
- **Socratic Experiential Learning**
- **Art-Led Reflection**

How the HIV CUREiculum is being co-created

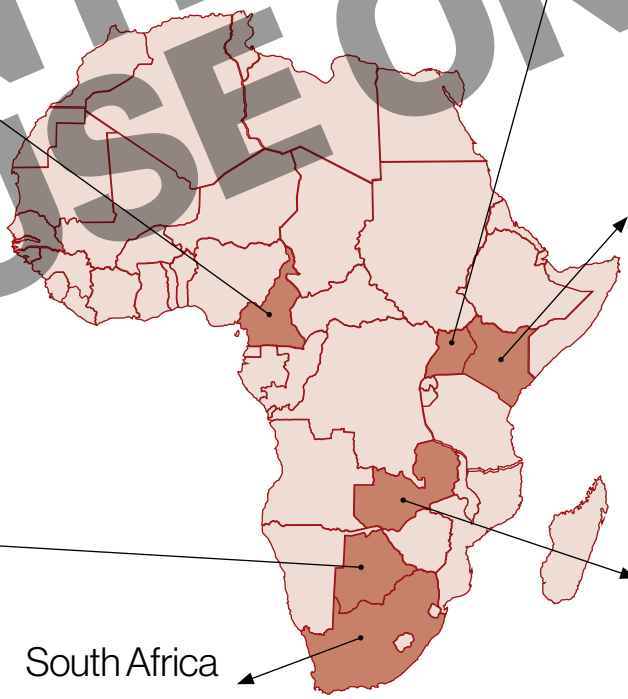
This CUREiculum is shaped as a shared journey led by community participants, the African Alliance team, clinical and scientific contributors from the AHCC, and our graphic and instructional designers.

The first draft of the CUREiculum was tested in community settings in Nairobi and Lusaka in 2025. Through a collaborative process, complex HIV Cure science became clear and accessible, creating a tool that honours community expertise and strengthens community-led advocacy. In 2026, the CUREiculum will be rolled out in the first five countries – Botswana, Cameroon, Kenya, South Africa and Uganda. Inputs from these sessions will be included for Edition 2 in 2026.

After 2026, we expect the CUREiculum will expand more widely across the continent to grow a diverse, powerful social movement of advocates for an HIV Cure.

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HIV prevalence refers to the proportion of adults (15–49) living with HIV at a given time, while HIV incidence refers to the number of new infections occurring in a year. These estimates are derived from national surveillance data and epidemiological modelling conducted by UNAIDS and WHO.



Uganda

A generalised epidemic with 5.2% adult prevalence, ~1.4 million people living with HIV, and ~38,000 new infections annually, with incidence relatively stable but slowly declining.

Cameroon

A generalised epidemic with concentrated key-population sub-epidemics, with 2.7% adult prevalence, ~480,000 people living with HIV, and ~23,000 new infections annually, with gradual but uneven declines.

Kenya

A generalised epidemic with strong regional variation, with 3.7% adult prevalence, ~1.4 million people living with HIV, and ~16,700 new infections annually, with incidence declining through expanded prevention and treatment.

Botswana

A high-burden generalised epidemic with 15.7% adult prevalence, about 380,000 people living with HIV, and ~4,300 new infections annually, with incidence steadily declining due to strong treatment coverage.

Zambia

A generalised epidemic with 11.1% adult prevalence, ~1.3 million people living with HIV, and ~33,000 new infections annually, with incidence declining alongside expanded treatment access.

South Africa

The largest HIV epidemic globally, with 18.3% adult prevalence, ~7.7 million people living with HIV, and ~150,000 new infections annually, within a large-scale generalised epidemic with gradually declining incidence.

Sources
UNAIDS. Global AIDS Update 2024–2025 and UNAIDS Country Epidemiological Profiles for Botswana, Cameroon, Kenya, South Africa, Uganda, and Zambia.

Module Structure

The following structure guides each of the module's development:

	5 mins	**Grounding** Facilitators ground the participants and outline the module goals and topics.
	3 hrs	**Content** Two sessions per day explain HIV Cure science in simple, visual ways.
	45 mins	**Activities** Fun and quick interactive exercises deepen learning.
	45 mins	**Teach-back** Participants share key points in short summaries.
	15 mins	**Reflection** The participants capture what worked and what should be improved.
	5 mins	**Knowledge check** A brief multiple-choice test for Monitoring, Evaluation and Learning (MEL) starts and ends each session

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PART 2

Modules

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Module 1

Introduction to and Rationale for an HIV Cure

- Why is HIV Cure Research needed?
- Key Terms used in HIV Research
- Who leads HIV Cure Research?
- What is an HIV Cure?
- Fourteen cases towards a HIV Cure
- Where is science towards a cure?

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Opening Session

60 mins	**PRELIMINARIES**	
	5 mins	**SPIRITUAL PAUSE**
	5 mins	**WELCOME BY THE HOST**
	30 mins	**KNOW YOUR PEERS**
	5 mins	**PRE-MODULE ASSESSMENT**
	5 mins	**INTRODUCTORY FRAMING AND LEARNING OUTCOMES**
	5 mins	**GROUNDING**

Core Content Session 1

PREAMBLE TO HIV CURE RESEARCH

2½ hrs

After this session, you will be able to:

- Provide reasons why an HIV Cure is worth investing in;
- Explain key terms used in HIV Cure science;
- Advocate for a community-led cure;
- Describe current pathways to an HIV Cure;
- Describe HIV Cure milestones already achieved and what lies ahead for future advocacy.

	75 mins	**Topic 1.1: Why do we need HIV Cure Research?**
		GROUP ROLEPLAY: BRIDGING PERSPECTIVES: COLLECTIVE CONVERSATIONS ABOUT AN HIV CURE
	15 mins	**SUGGESTED 15-MINUTE BODY BREAK HERE**
	60 mins	**Topic 1.2: Key Terms in HIV Cure Research**
		SMALL GROUP ACTIVITY: KEY TERMS USED IN HIV CURE RESEARCH

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	HANDOUT: MODULE 1: KEY TERMS IN HIV RESEARCH
	FLIPCHART/POSTER: GAME INSTRUCTIONS FOR EACH-ONE-TEACH-ONE (PREPARE BEFORE IF POSSIBLE)

Core Content Session 2

3h 50 mins PATHWAYS TO AN HIV CURE

75 mins Topic 1.3: What is an HIV Cure?

	GROUNDING
	HANDOUT HIV INFECTION LIFE-CYCLE HANDOUT WITH ANNOTATIONS ON OPPORTUNITIES FOR THE CURE PATHWAYS
	ACTIVITY Model the HIV life cycle using play dough or by drawing each of the components. Use the 9 steps in the annotated illustration of the HIV life cycle in the Toolbox.
60 mins	SUGGESTED 15-MINUTE LUNCH BREAK HERE

50 mins Topic 1.4: 14 Cases of HIV Cure, Post-, Elite, and Exceptional-Elite Controllers

	GROUNDING
	ACTIVITY IN 8-10 PAIRS: 14 CASES TOWARDS AN HIV CURE
	HANDOUT: Case studies of 14 Cases of HIV Cure, Post-treatment and Elite-Controllers
	FLIPCHART: PAIR QUESTIONS TO ANALYZE 14 CASES TOWARDS AN HIV CURE
	PLENARY FEEDBACK

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	30 mins	**Topic 1.5: Where is Science regarding an HIV Cure?**
		GROUNDING
		SESSION CONTENT & PLENARY DISCUSSION
	15 mins	**SUGGESTED 15-MINUTE BODY BREAK HERE**

Closing Session

40 mins		**MODULE ROUND-UP**
	20 mins	**TEACH-BACK: UNDERSTANDING HIV CURE** • Why we need an HIV Cure • The language used to advocate for a Cure • What a cure looks like as a product (TPP) and a process (current possibilities) • 14 cure cases • Where is the science regarding a cure for everybody that is logistically feasible for low- and middle-income countries
	5 mins	**POST-MODULE ASSESSMENT**
	5 mins	**HOMEWORK ASSIGNMENT** 1. Place HIV Cure in the middle and add bubbles of different concepts and sub-concepts learnt during this module 2. Add concept map to gallery wall for Day 2 Recap
	5 mins	**CLOSING NOTES**
	5 mins	**SPIRITUAL PAUSE**

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Module 2

Ethics & Leadership in HIV Cure



- What is 'Ethics'
- Key Terms used in Research Ethics
- The last 100 years of Ethics in Biomedical Research
- Overview of Ethical Guidelines

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Opening Session

60 mins PRELIMINARIES

5 mins	SPIRITUAL PAUSE TO OPEN
30 mins	WELCOME BY THE HOST
10 mins	PRE-MODULE ASSESSMENT
10 mins	INTRODUCTORY FRAMING AND LEARNING OUTCOMES
5 mins	GROUNDING

Core Content Session 1

PREAMBLE TO HIV CURE RESEARCH ETHICS

3 hrs

After this session, you will be able to:

- Explain the concept and importance of research ethics
- Engage with research ethics language
- Describe the history and development of ethical guidelines
- Apply ethical considerations to their own context and future research

55 mins	**Topic 2.1: What is 'ethics'?**
15 mins	SUGGESTED 15-MINUTE BODY BREAK HERE
50 mins	**Topic 2.2: Key Terms used in Research Ethics**
	LARGE GROUP ACTIVITY Match the definition competition. Refer to Module 2 Key Terms used in Research Ethics
	HANDOUT: MODULE 2: KEY TERMS IN RESEARCH ETHICS

INTERNAL USE ONLY

		COMPETITION: GAME INSTRUCTIONS FOR MATCH-THE-DEFINITION (
		SELF-REFLECTION
	60 mins	SUGGESTED 60-MINUTE LUNCH HERE
	60 mins	**Topic 2.3: The Last 100 years of Ethics in Biomedical Research**
		HANDOUT: RESEARCH ETHICS CASE STUDIES
		FLIPCHART/POSTER: CASE ETHICS CASE STUDY PRESENTATIONS WITH GROUP QUESTIONS
		SMALL GROUP ACTIVITY: ETHICS CASE STUDY PRESENTATIONS

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Core Content Session 2

ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH

2¾ hrs

There are a number of ethics guidelines that influence clinical trials protection. These include standalone guidelines, trial network guidelines and IRB/Regulatory conditions. In this module we highlight three key guidelines, but acknowledge that these will be used in addition to country-level guidelines and regulatory conditions or standards.

	75 mins	**Topic 2.4: Overview of Ethical Guidelines**
		FLIPCHART/POSTER: ETHICS GUIDELINES DISCUSSION QUESTIONS
		HANDOUT: SCIOMS, GPP & ALLEA GUIDELINE SUMMARIES AND LINK TO FULL PDF
		SMALL GROUP ACTIVITY
	60 mins	SUGGESTED 60-MINUTE BODY BREAK HERE

Closing Session

1¾ hrs MODULE ROUND-UP

20 mins	**TOPIC REFLECTION AND FEEDBACK FROM PARTICIPANTS**
5 mins	**POST-MODULE ASSESSMENT**
15 mins	**SUGGESTED 15-MINUTE BODY BREAK HERE**
50 mins	**TEACH-BACK** Elevator pitch for improving ethics in a pharmaceutical manufacturing facility.
5 mins	**CLOSING NOTES**
5 mins	**SPIRITUAL PAUSE**

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Module 3

HIV Persistence and HIV Cure Strategies

- What Is HIV Persistence
- Key Terms in HIV Persistence & Cure Pathway
- What are scientists considering for an HIV Cure?
- Four Emerging Cure Strategies: A deep dive

INTERNAL USE ONLY



Opening Session

60 mins PRELIMINARIES

5 mins	SPIRITUAL PAUSE TO OPEN PROCEEDINGS
10 mins	WELCOME
10 mins	RECAP FROM DAY 2
5 mins	PRE-MODULE ASSESSMENT
5 mins	INTRODUCTORY FRAMING AND LEARNING OUTCOMES
5 mins	GROUNDING

Core Content Session

HIV CURE STRATEGIES

5¼ hrs

After this session, you will be able to:

- Describe HIV Persistence
- List how current scientific research translates into four Cure Pathways
- Describe what can be expected from HIV Cure research in the future

15 mins	**Topic 3.1: What is HIV Persistence?**
30 mins	**Topic 3.2: Key Terms used in HIV Persistence & Cure Pathways**
	HANDOUT: MODULE 1: KEY TERMS IN HIV PERSISTENCE AND CURE PATHWAYS
	FLIPCHART/POSTER: GAME INSTRUCTIONS FOR EACH-ONE-TEACH-ONE
	SELF-REFLECTION
30 mins	SUGGESTED 30-MINUTE BODY BREAK HERE

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	3hrs	**Topic 3.3: Four Emerging Cure Strategies: A Deep Dive**
		SESSION CONTENT & PLENARY DISCUSSION
		FLIPCHART: TEACH-BACK QUESTIONS – PREPARE BEFORE FOR EACH GROUP
		SMALL GROUP ROLEPLAY ACTIVITY: CASE STUDIES FOR CURE PATHWAYS
	60mins	**SUGGESTED 60-MINUTE BODY BREAK HERE**



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Closing Session

1¾ hrs MODULE ROUND-UP

	60 mins	**TEACH-BACK**
	10 mins	**TOPIC REFLECTION**
	15 mins	**SUGGESTED 15-MINUTE BODY BREAK HERE**
	5 mins	**HOMEWORK ASSIGNMENT TO AUGMENT LEARNING** The extensive technical detail in Module 3 and 4 will require community advocates to adapt typical community engagement tactics to accommodate the demands of HIV Cure Research Introduction into communities in and around trial sites, as well as for core community stakeholders for HIV Cure research. Using the Learning Toolbox template, develop an action list for your context/setting that identifies how to introduce HIV Cure Strategies IN GENERAL to your constituency. These action lists will be displayed on the gallery wall for a morning walkabout to recap (this generality is important, as it links with tomorrow's homework).
	5 mins	**HANDOUT: MODULE 3 HOMEWORK ASSIGNMENT**
	5 mins	**CLOSING NOTES**
	5 mins	**SPIRITUAL PAUSE**

INTERNAL USE ONLY

Module 4

HIV Cure Trials: History and Future



- The history of Cure Trials
- Anticipated Cure trials by 2030
- Analytical Treatment Interruption

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Opening Session

60 mins PRELIMINARIES

5 mins	SPIRITUAL PAUSE TO OPEN PROCEEDINGS
10 mins	WELCOME BY THE HOST
10 mins	RECAP FROM DAY 3
5 mins	PRE-MODULE ASSESSMENT
5 mins	INTRODUCTORY FRAMING AND LEARNING OUTCOMES
5 mins	GROUNDING

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Core Content Session

HIV CURE TRIALS

5 hrs

After this session, you will be able to:

- Recount the history of HIV Cure Research
- Describe what we can expect from HIV Cure Research in the next decade
- Reflect on HIV Cure trial leadership now and in the future

75 mins	**Topic 4.1: The History and future of HIV Cure Trials**
	HANDOUT: THE HISTORY OF HIV CURE TRIALS
	PAIRED GROUP ACTIVITY: HIV CURE TRIALS
15 mins	SUGGESTED 15-MINUTE BODY BREAK HERE
1½ hrs	**Topic 4.2: Anticipated Cure Trials by 2030** What's the current landscape? HIV cure trials are becoming safer, fairer, and more focused on community needs.

	1½ hrs	**Topic 4.3: What is an Analytical Treatment Interruption?**
		HANDOUT: ANALYTICAL TREATMENT INTERRUPTIONS
		GROUP ROLE PLAY: THE ATI REVIEW IN THE COMMUNITY ADVISORY BOARD
	60 mins	SUGGESTED 60-MINUTE BODY BREAK HERE

Closing Session

	2 hrs	**MODULE ROUND-UP**
	60 mins	COLLABORATIVE TEACH-BACK ON ANALYTICAL TREATMENT INTERRUPTION
	30 mins	TOPIC REFLECTION
	5 mins	POST-MODULE ASSESSMENT
	15 mins	SUGGESTED 15-MINUTE BODY BREAK HERE
	5 mins	CLOSING WITH SPEAKING NOTES
	5 mins	SPIRITUAL PAUSE

INTERNAL USE ONLY



- What is an analysis?
- What does it mean tointerrupt something?
- What reasons can you think of for interrupting treatment?
- What do you think will happen if HIV treatment is interrupted?

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Module 5

The role of Communities, Stakeholders and Patients in HIV Cure Strategies

- What is 'leadership' in Clinical Trials?
- People-led Partnerships
- Bringing Community & Leadership together

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Opening Session

PRELIMINARIES (60 mins)

5 mins	SPIRITUAL PAUSE TO OPEN
10 mins	WELCOME BY THE HOST
30 mins	RECAP FROM MODULE 4
5 mins	PRE-MODULE ASSESSMENT
5 mins	INTRODUCTORY FRAMING AND LEARNING OUTCOMES
5 mins	GROUNDING

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Core Content Session

COMMUNITY LEADERSHIP

4¾ hrs

After this session, you will be able to:

- Centre the community in HIV Cure advocacy
- Reflect on HIV Cure trial leadership now and in the future
- Describe elements of what community-engaged HIV Cure research looks like

Topic 5.1: What is 'Leadership' in Clinical Trials

60 mins

Leadership structures in clinical trials are important because they shape **who gets heard, who is included, and who benefits** from the research.

When leadership is intentional about **diversity, equity and inclusion (DEI)**, trials are more likely to involve people who have been left out in the past, respond to real community needs, and produce results that work for everyone – not just a few.

60 mins	FOCUSED DISCUSSION TO DEFINE MEANINGFUL ENGAGEMENT
15 mins	SUGGESTED 15-MINUTE BODY BREAK HERE

	60 mins	**Topic 5.2: People-led partnerships**
		SMALL GROUP ACTIVITY: MEETING THE COMMUNITY WHERE YOU FIND IT
	45 mins	**Topic 5.3: Bringing Community & Leadership together**
	60 mins	SUGGESTED 60-MINUTE BODY BREAK HERE

Closing Session

60 mins		**MODULE ROUND-UP**
	30 mins	ASSESSMENT: 2 000-WORD ESSAY (1-2 WEEKS)
	25 mins	TOPIC REFLECTION
	5 mins	POST-MODULE ASSESSMENT
	5 mins	ENGAGEMENT ON NEXT STEPS
	5 mins	TRAINING ASSESSMENT: 2,000-WORD ESSAY
	5 mins	ACKNOWLEDGEMENTS & CLOSE
	5 mins	SPIRITUAL PAUSE

INTERNAL USE ONLY

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PART 3

Toolbox

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Module 1 Key Messages

Why is HIV Cure research needed?

- **Living with HIV is a chronic condition** that requires taking regular medication and attending healthcare facilities[1] frequently: PLHIV must take daily medication (ART) and see a healthcare worker at a facility every month, or every second or third month. There are times when this can be an obstacle, for example, when travelling or moving locations, when shifts at work change or when visiting relatives.

- **Stigma Around Taking HIV Medication:** The burden of medication for HIV can make people feel ashamed or different, leading to social isolation and emotional stress. These factors themselves affect how motivated people are to take medication every day.

- **Annoyance at Taking Pills Every Day:** Otherwise known as pill or treatment fatigue, most chronic and long-term medications become difficult to continue using correctly and consistently, especially when the patient is feeling healthy.

- **Unknown Effects from Long-Term Medication:** Antiretroviral medication is still being monitored; we are still collecting evidence on how it affects people over many years. There can be side effects from long-term use. This is starting to emerge from older people on ART who can also experience unexpected symptoms associated with the physical changes in the body that occur later in life, and how this interacts with ART.

- **High Cost of Long-Term Medication:** Providing daily HIV medication to over 38 million people around the world for their entire lives is extremely expensive and complicated to sustain, especially in poorer countries.

- **Health Risks Despite Treatment:** Even with treatment, the immune system can act unexpectedly differently, damaging essential organs such as the brain and heart.

- **Risk of Passing on HIV:** While treatment dramatically reduces the chance of spreading HIV, it doesn't completely eliminate the risk of acquisition. A cure is needed to entirely stop the virus from being transmitted.

- **Drug Resistance:** over time, HIV can become drug resistant, which contributes to more people acquiring HIV.

- **Public Health Disruptions and Uncertainty:** which can affect medication availability and service access (COVID, PEPFAR, USAID) for example, election cycles, drug stock-outs, embargoes, emergencies, diplomatic events, political action, community conflicts, disruptive weather and labour protests, to name a few.

- **Inconsistent Access to Treatment:** There are PLHIV who don't have consistent access to treatment, such as internally displaced people and refugees, sex workers, freight workers, and people socially excluded from mainstream access.

INTERNAL USE ONLY

Why do we need HIV Cure Research?

1. Living with HIV is a chronic condition
2. Lifelong ART is effective and improving all the time
3. There is stigma in HIV Medication
4. Annoyance at taking pills every day
5. Unknown effects from long-term medication
6. High cost of long-term medication
7. Health risks treatment
8. Risk of passing on HIV
9. Drug resistance
10. Public health disruptions and uncertainty
11. Inconsistent access to treatment
12. Uneven access to treatment for complex populations

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Module 1

Key Terms in HIV Cure Research

1. **Antibodies** – Proteins the immune system makes that help find and destroy viruses such as HIV.
2. **ART (Antiretroviral Therapy)** – Medication that people with HIV take daily to stop the virus from making more copies of itself, keeping them healthy but not curing the disease.
3. **Berlin Patient / London Patient** – The nicknames for two people who were cured of HIV after receiving bone marrow transplants; however, this method is risky, and not suitable for everyone.
4. **Bone Marrow Transplant** – A medical procedure in which a person receives healthy bone marrow from a donor, which has sometimes led to a cure for HIV in a few rare cases.
5. **Community Advocacy** – Efforts by people in local communities to push for better treatments, more research, and a cure for HIV.
6. **Community Translation** – Making complex scientific information about HIV Cure research more accessible to understanding and relevant to people in local communities.
7. **Durable Viral Control** – A situation in which someone with HIV can live without medication because the virus remains under control and doesn't cause harm.
8. **FRESH Study** – A research study in South Africa that looks at how early treatment might help cure HIV, especially in young women at high risk.
9. **Gene Therapy** – A cutting-edge treatment that changes a person's genes to help their body fight off diseases such as HIV.
10. **Global Gene Therapy Initiative (GGTI)** – A worldwide collaboration of scientists working on using gene therapy to find a cure for HIV.
11. **HIV Antiviral Treatment** – The medication used to control HIV and keep people healthy, but which doesn't completely cure the infection.
12. **HIV Control Without Daily Drugs** – When a person with HIV doesn't need to take medication every day because their body can keep the virus under control.
13. **HIV Cure Research** – The scientific study aimed at finding a way to eliminate or control HIV in a person's body, so they no longer need lifelong treatment.
14. **HIV Cure Strategies** – The different scientific methods being researched to cure HIV, such as removing the virus entirely or keeping it under control without daily treatment.
15. **HIV DNA** – The genetic material of HIV that hides inside human cells, making it difficult to eliminate.
16. **HIV Replication** – The process of making copies of itself inside the body.
17. **HIV Reservoir** – Parts of the body where HIV hides and stays inactive, such as the brain or bone marrow, making it hard to cure.
18. H**IV Reservoir Sites** (brain, lymph nodes, gut, bone marrow, genital tract) – The places in the body where HIV can hide and stay inactive, even when a person is on medication.

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19. **HIV-1 Proviruses** – A form of HIV that stays hidden inside a person's cells and can reactivate later, even if it's not currently making copies.

20. **Immunotherapy** – A type of treatment that uses the body's immune system to fight diseases like HIV.

21. **Latent Reservoir** – The places in the body where HIV hides and stays inactive, making it difficult to cure the infection entirely.

22. **Latently Infected Cells** – Cells that are infected with HIV but are not actively producing the virus, making the infection hard to detect and cure.

23. **Long-Acting Treatments** – New forms of HIV medication that people can take less frequently, e.g. once every few months instead of daily.

24. **Memory Cells** – Special cells in the body that 'remember' infections like HIV and help the immune system respond to them, but which can also hide the virus.

25. **Replication-Competent Proviruses** – HIV that is hidden but can still start making new copies of itself if it 'wakes up' inside the body.

26. **Treatment Interruption** – When someone with HIV stops taking their medication temporarily, usually as part of a controlled experiment to see if their body can control the virus on its own.

27. **U=U (Undetectable = Untransmittable)** – A concept which means that when a person's HIV levels are undetectable with medication, they cannot pass the virus to others.

28. **Viral Clearance** – A potential way to cure HIV by completely removing all traces of the virus from a person's body.

29. **Viral Load** – The amount of HIV in a person's blood. A lower viral load means the virus is better controlled.

30. **Viral Rebound** – When HIV comes back and starts making more copies after someone stops taking their medication.

31. **Viral Suppression** – When the amount of HIV in a person's blood is so low that tests can't detect it, but the virus is still in the body and could come back if treatment stops.

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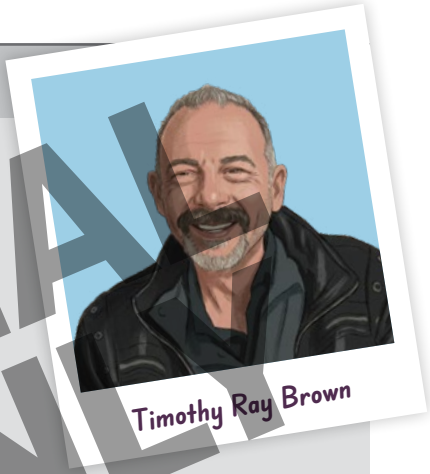
Module 1

Fourteen Cases of HIV Cure

COMPLETE/CLASSIC HIV CURE CASES

1. The first person cured of HIV[5] was Timothy Ray Brown

- American then living in Berlin, who received two stem cell transplants to treat leukaemia in 2006.
- The donor had double copies of a rare gene mutation on T-cells, the gateway most types of HIV use to infect cells.
- He underwent intensive conditioning chemotherapy and whole-body radiotherapy to kill off his cancerous immune cells, allowing the donor stem cells to rebuild a new HIV-resistant immune system.
- Brown survived for 14 years from the date of his bone marrow transplant without any sign of HIV returning.
- He died in September 2020[6] at the age of 54, of the leukaemia that first prompted his treatment.



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2. A second case was reported in 2019[7]: Adam Castillejo

- The 'London patient' received a stem cell transplant from a donor with natural resistance to infection as part of treatment for Hodgkin lymphoma.
- He stopped antiretroviral treatment 16 months after the transplant, by which time all his CD4 cells lacked CCR5 receptors.



3. The 'New York patient' was described in February 2022[8]

- She was notable for being the first female case, and as of that date had been 14 months off ART without her HIV returning.
- She received a haplo-cord blood transplant to treat leukaemia in 2017, using cells from more than one donor.
- This procedure was necessary because the woman was of mixed race, and the mutation that confers immunity to HIV is found almost solely in people of white European ancestry.

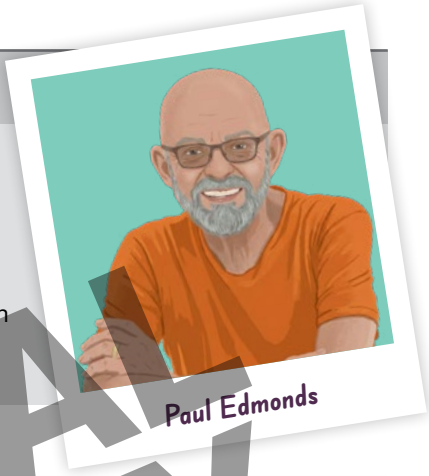
5. http://www.aidsmap.com/Stem-cell-transplant-has-cured-HIV-infection-in-Berlin-patient-say-doctors/page/1577949/
6. https://www.nytimes.com/2020/09/30/health/timothy-ray-brown-first-patient-cured-of-hiv-dies-at-54.html
7. https://www.aidsmap.com/news/mar-2019/london-patient-long-term-hiv-remission-after-stem-cell-transplant
8. https://www.aidsmap.com/news/feb-2022/new-york-woman-free-hiv-14-months-after-stem-cell-transplant

4. Marc Franke, the 'Düsseldorf patient'



- Received a stem cell transplant to treat leukaemia from a donor immune to HIV in 2013. More cautious than Castillejo, he did not stop taking ART until November 2018.
- His remission from HIV was first announced[9] at the same time as Castillejo's in 2019, although it attracted little attention at the time.
- In February 2023, after more than four years of extensive testing,[10] his doctors declared him cured of HIV.
- At CROI 2022, Professor Yvonne Bryson from the University of California Los Angeles spoke about the 'New York patient'.

5. Paul Edmonds, the 'City of Hope patient'



- As reported in July 2022, he received a stem cell transplant to treat leukaemia[11] from a donor with an immune cell mutation.
- He is the oldest person so far to experience viral control without treatment (63 years), has been living with HIV the longest (31 years), and has the lowest CD4 nadir (below 100).
- He stopped ART two years after his transplant and has shown no trace of HIV in the 17 months since, with his leukaemia also in remission.

6. Romuald, a French Swiss man[12] initially known as the 'Geneva patient'

- Was diagnosed with HIV in 1990 at the age of 18 and had been taking antiretroviral treatment which fully suppressed HIV since 2005.
- He received the transplant after chemotherapy and radiotherapy to treat leukaemia.
- Host CD4 cells were completely replaced within a month of the transplant, but he had graft-versus-host disease, which occurs when donor immune cells attack the recipient's body.
- This required treatment with ruxolitinib, a JAK 1/2 inhibitor, which has also been shown to reduce the size of the HIV reservoir[13].

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POST-TREATMENT CONTROLLERS

- The group of people referred to as post-treatment controllers had received very early antiretroviral treatment – within the first two weeks after acquiring HIV. Their blood results show that they are able to control HIV replication in the body.
- This sometimes allows to 'get ahead' of HIV's ability to settle in the reservior tisse in enough volume to rebound later.
- It has been found that this is possible because some people have nuetralising antibodies created naturally in their body.
- Scientists are trying to copy this action and are investigating how broadly neutralising antibodies, produced in a laboratory with the same properies as in the antobodies found in the post-treatment controllers, can succesfully ward off HIV settlement in the reservoir.[14] This strategy usually only works if people are treated very early, and it only produces long-term viral control in a fraction of trial participants, such as a number of patients in France[15], the US[16] and Germany[17].

9. https://www.croiconference.org/abstract/analytic-treatment-interruption-ati-after-allogeneic-ccr5-d32-hsct-aml-2013/
10. https://www.aidsmap.com/news/feb-2023/german-man-remains-free-hiv-nearly-10-years-after-stem-cell-transplant
11. https://www.aidsmap.com/news/aug-2022/california-man-appears-be-another-person-cured-hiv-after-stem-cell-transplant
12. https://www.aidsmap.com/news/jul-2023/first-person-may-be-cured-hiv-after-stem-cell-transplant-without-ccr5-mutation
13. https://www.aidsmap.com/news/aug-2023/immune-modulating-medication-may-help-clear-hiv-reservoir
14. https://www.science.org/doi/10.1126/scitranslmed.abq4490
15. https://www.aidsmap.com/news/mar-2013/french-researchers-report-14-patients-remission-after-controlling-hiv-over-4-years
16. https://www.aidsmap.com/news/aug-2018/one-nine-people-may-be-able-control-their-viral-load-after-stopping-treatment-us
17. https://www.aidsmap.com/news/jul-2013/german-researchers-report-case-functional-cure-after-very-early-hiv-treatment

7. In 2022, the latest report on the French 'VISCONTI' cohort[18] identified six men and four women who started a course of ART within three months of infection, and subsequently stopped it; in this cohort the virus has remained undetectable, and they have not re-started treatment.

- Seven of the ten have now remained undetectable for more than ten years, including one man who stopped treatment 17 years ago.
- Children started early on ART are thought to be especially good candidates for post-treatment control as they can be started on ART very soon after infection, and they have fewer effector-memory T-cells, which are the type that become latent and hide HIV.

8. A study of 281 mother-infant pairs identified five South African boys who had controlled HIV[19]:

- All infants in the study who had acquired HIV received antiretroviral treatment after delivery, and 92% were also exposed to the medication in the womb.
- Infants had been off antiretroviral treatment for between three and 19 months at the time the study reported its findings.
- The study suggests that there may be a gender difference in HIV control in infants, as girls are less likely to have HIV sensitivity to type 1 interferon because they produce higher levels of type 1 interferon during gestation.

9. Another case of HIV control after discontinuing treatment in a child treated soon after birth was reported in 2020[20].

- A child in Texas started treatment within two days of birth, had a positive HIV DNA test two weeks after birth and discontinued treatment at the age of 13 months.
- Three years later the child had undetectable HIV RNA, and HIV DNA was detectable at extremely low levels intermittently during the follow-up period.
- In 2013, the 'Mississippi baby' – who received antiretroviral treatment from very soon after birth – was reported. Treatment stopped after 18 months as the mother and baby stopped attending the clinic.[21] HIV DNA was undetectable five months later, when the mother and baby returned to the clinic, and HIV remained undetectable for 27 months before viral load rebound occurred[22].

INTERNAL USE ONLY

18. https://www.nature.com/articles/s41467-022-29511-1
19. https://www.aidsmap.com/news/jul-2023/hiv-treatment-womb-helped-five-south-african-baby-boys-stay-undetectable-therapy
20. https://www.aidsmap.com/news/mar-2020/child-hiv-maintains-viral-suppression-three-years-treatment
21. https://www.aidsmap.com/news/mar-2013/case-report-functional-hiv-cure-child
22. https://www.aidsmap.com/news/jul-2014/reappearance-hiv-mississippi-baby-poses-questions-early-treatment

10. The 'Buenos Aires patient'[23] had not received treatment in early infection, and there was nothing particularly advantageous in her medical history such as a consistently low viral load.

- When diagnosed in 1996, she had a low CD4 count (160) and at least one AIDS-related illness (toxoplasmosis).
- Her viral load, initially 2 200, rose to 36 000 a year later due to adherence difficulties; but after switching her ART regimen, she never had a detectable viral load again – despite stopping ART in 2007 due to side effects.
- When her case was reported in 2021, she had been off ART with an undetectable viral load for at least 12 years.
- Investigations in 2015 and 2017 could not find any replication-competent HIV DNA in 2.5 billion white blood cells, and an upper limit of one unit of intact viral DNA in 390 million CD4 cells.
- Though her CD4 cells retained immune responses to HIV, her CD8 cells had very weak responses. Unusually, even for HIV controllers, she is now HIV negative, having lost her antibodies to the virus.
- This woman does have HLA B*57, a genetic variant associated with lower viral loads and slow progression, but it does not seem to have stopped her developing a severe HIV infection in the first place.
- Exactly how she has managed to control her HIV so profoundly remains a mystery, but her 'Sero reversion' – disappearance of antibodies – and her sluggish CD8 response do seem to be extreme examples of processes seen in some other post-treatment controllers.[24]

11. The Barcelona patient has controlled HIV for more than 15 years without treatment[25].

- Diagnosed with HIV during acute infection, she received four different immune-modulating drugs in addition to her normal antiretroviral treatment, as part of a clinical trial[26].
- However, she was the only person out of 20 participants in the trial to maintain long-term viral control off ART, so it is difficult to know whether to ascribe her control to the extra treatment or to possible elite control;
- Research confirmed[27] that she most probably controlled viraemia well because of a combination of factors:
- Very early antiretroviral treatment (she started drugs in the first weeks of infection, before the virus built big hide-outs);
- Plus, a short course of immunomodulating trial drugs;
- A lucky genetic set-up that already favoured strong NK-cell activity against viruses;
- A quiet, chronic CMV (herpesvirus) infection that further 'primed' those same NK cells to stay on alert.

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ELITE CONTROLLERS

- Few people with HIV can control viraemia without HIV medication.
- People who can maintain viral loads between 50-2 000 copies without treatment are known as elite or viraemic controllers.
- In the US and UK, less than 4% of people with HIV are considered viraemic controllers.
- Surprisingly, a recent study identified that 13% of people in the South African and Zambian PopART cohort were viraemic controllers[28].
- This is higher than in the US and UK studies, and most of the viraemic controllers identified in the PopART cohort were women.
- Some studies suggest that women might be more likely to control HIV without medication compared to other groups, but these studies are limited and require further investigation.
- Understanding how sex differences and other factors may contribute to viraemic control has the potential to inform cure strategies.
- 'Exceptional elite controllers' maintain undetectable viral loads because their immune system seems to have eliminated all intact viral material from their bodies.

23. https://www.aidsmap.com/news/feb-2021/buenos-aires-patient-argentinian-woman-controls-hiv-least-12-years-after-stopping
24. https://www.aidsmap.com/news/dec-2019/will-post-treatment-controllers-guide-us-towards-hiv-cure
25. https://www.aidsmap.com/news/aug-2022/barcelona-woman-controls-hiv-over-15-years-without-treatment
26. https://clinicaltrials.gov/ct2/show/NCT00979706
27. https://www.natap.org/2022/IAC/IAC_73.htm
28. https://www.aidsmap.com/news/nov-2023/nearly-13-participants-african-cohort-maintain-hiv-control-treatment

12. Loreen Willenberg is a Californian woman considered to be an exceptional elite controller.



- She was diagnosed with HIV in 1992 at the age of 37.
- From the start she maintained a high CD4 count and undetectable viral load since diagnosis (except for one viral blip).
- She volunteered for studies of long-term non-progressors (people who maintain intact immune systems without treatment) and in 2011 learned that scientists could find no replication-competent HIV in her immune cells.

13. 'The Esperanza patient'[29] is another example of an exceptional elite controller. This woman is named after her hometown in Argentina.

- Diagnosed at the age of 21 in 2013, she took one six-month course of ART during pregnancy in 2020 to safeguard her baby, but has never otherwise been on ART and has not had a detectable viral load test in nine years.

14. The Australian man who appears to have cleared his own infection.[30]

- He had a rare combination of factors (a defective virus, one of his two CCR5 co-receptor genes missing, and a response to HIV characteristic of slow progressors) that most people with HIV would not share.
- However, these factors did appear to have given his body more time than usual to mount a strong CD8 response, and a specific CD4 response, to HIV.
- This is the kind of immune response researchers would like to replicate in other people.

INTERNAL USE ONLY

29. https://www.aidsmap.com/news/nov-2021/has-another-woman-naturally-cleared-hiv
30. https://www.aidsmap.com/news/jun-2019/unique-case-australian-man-appears-have-cleared-his-hiv-infection

The differences between Post-Treatment Controllers and Elite Controllers



POST-TREATMENT CONTROLLERS

This group received very early antiretroviral treatment – within the first two weeks after acquiring HIV

- They are able to control HIV replication in the body after treament
- Nuetralising antibodies created naturally in their bodies
- Scientists are trying to copy this action



ELITE CONTROLLERS

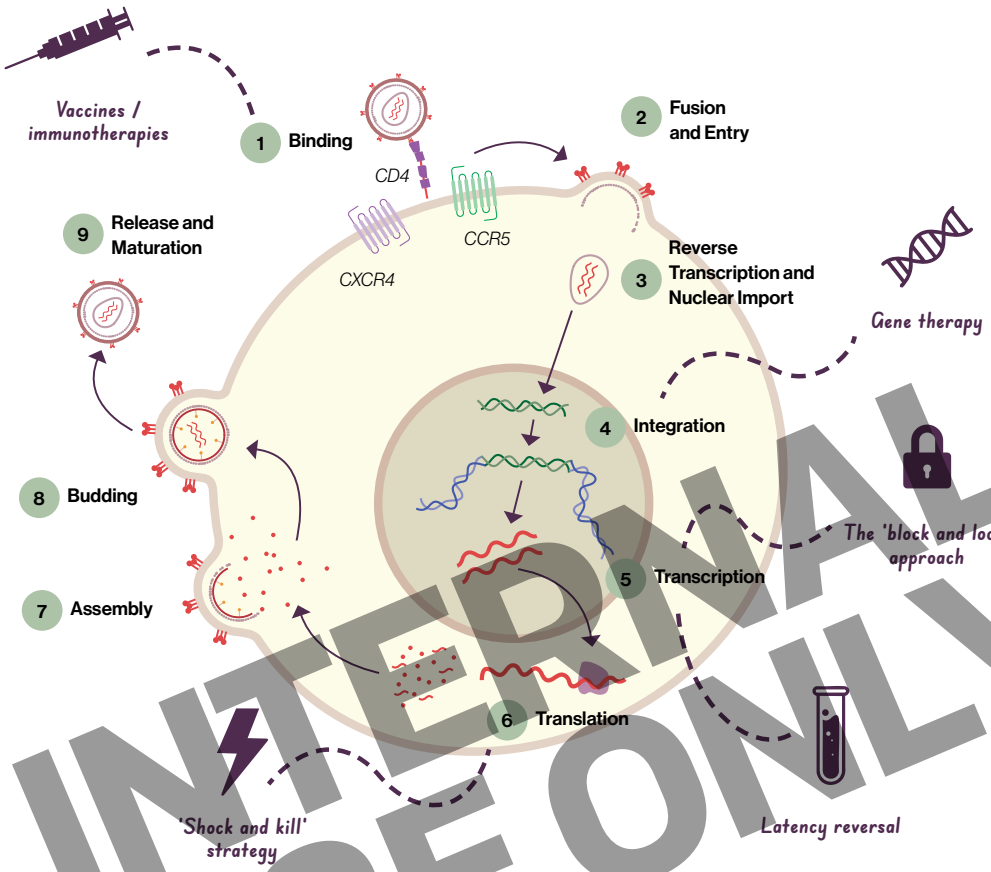
This group maintains undetectable viral loads because their immune system seems to have eliminated all intact viral material from their bodies

- People who can maintain viral loads between 50-2 000 copies without treatment are known as elite or viraemic controllers
- Can control viraemia without HIV medication
- Some studies suggest that women might be more likely to control HIV without medication

INTERNAL USE ONLY

Module 1

HIV Life-Cycle



INTERNAL USE ONLY

1. Binding

HIV begins infection by attaching itself to the surface of a CD4 immune cell also called the host cell.

2. Fusion and Entry

After binding, the virus releases its genetic material (RNA) into the cell. The virus doesnt have its one DNA which dictates cell replication.

3. Reverse Transcription

Using an enzyme called reverse transcriptase, the virus converts its RNA into DNA.

4. Nuclear Import and Integration

The newly formed viral DNA enters the host cell nucleus and inserts itself into the cell's DNA. Once integrated, HIV becomes part of the cell's genetic instructions.

5. Transcription

The infected cell reads the viral DNA and produces new viral RNA.

6. Translation

The cell's machinery uses this RNA to produce viral proteins, which are the building blocks needed to make new virus particles.

7. Assembly

New viral RNA and proteins come together inside the cell to form immature HIV particles.

8. Budding

The new virus particles push out through the cell membrane and leave the infected cell.

9. Release and Maturation

After leaving the host cell, the virus matures into a fully infectious virus, ready to infect other CD4 cells.

Module 2

Key Terms in HIV Cure Research Ethics

1. **Informed Consent –** This means you choose to join a study only after everything has been explained clearly: what the study is about, what will happen, possible risks, and that you can stop at any time.
2. **Voluntary Participation –** You join because you want to, not because anyone pressures you. Your 'yes' or 'no' must always be respected.
3. **Community Engagement –** Researchers work with the community – not on their own – to design, run and share information about HIV Cure studies.
4. **Cure-Related Treatment Interruption (ATI) –** A planned break from HIV treatment (ART) during a study so researchers can see how well a cure strategy works. This is done under close medical supervision.
5. **Viral Rebound –** When HIV levels in the blood rise again after stopping ART. Because this can happen quickly, people in ATI studies are monitored very closely.
6. **Privacy & Confidentiality –** Your personal information — including your HIV status — must be kept safe; nothing is shared without your permission.
7. **Stigma & Social Harm –** Researchers must protect participants from any harm, including gossip, judgement, discrimination, or added stigma.
8. **Therapeutic Misconception –** When someone thinks a study is the same as medical treatment. 'Research tests ideas for the future – it is not guaranteed to help you directly.'
9. **Risk-Benefit Balance –** Researchers must make sure that any risks in a study are as small as possible, and that the potential benefits for the community are clear.
10. **Autonomy –** Your right to make your own choices about your body, your health, and your involvement in research.
11. **Justice –** Everyone should have a fair chance to take part in research and benefit from what it produces – especially communities most affected by HIV.
12. **Safe Monitoring –** During a study, your health is checked often so that any issues can be caught early and treated quickly.
13. **Post-Trial Access –** If something in the study helps you, there must be a plan so you can continue getting that support or treatment afterwards.
14. **Benefit Sharing –** Communities involved in research should gain something meaningful – such as better information, skills, opportunities, or health services.
15. **Respect for People Living with HIV (PLHIV) –** HIV cure studies must never increase stigma, shame or blame. Research must honour people's dignity, experiences and leadership.
16. **Post-trial Access –** equitable and fair access to approved medicine products for all people living with HIV.

INTERNAL USE ONLY

Module 2

Research Ethics Case Studies

The Denver Principles

The Declaration of Helsinki

Nazi Experiments during WW2

The Tuskegee Syphilis Study

The Tenofovir Prep Trials

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The Denver Principles[31]

Drawn up in Denver in 1983, the Principles outlined rights and responsibilities for PLHIV and provided recommendations for healthcare professionals, family, and friends. "The Denver Principles were the foundation of the GIPA Policy, which placed us, PLHIV, at the centre of the response."

The Declaration of Helsinki[32]

In 1964, in Helsinki, the World Medical Association (WMA) declared their response to concerns regarding research on patient populations during the Second World War. The primary purpose of the accord was to assert the interests of the individual patient before those of society.

The Declaration of Helsinki is intended to prevent mistreatment of human subjects, a principle also recognised in the Nuremberg Code. It guides researchers, scientists and physicians conducting clinical research to protect human subjects and their communities during such clinical research.

Below is an excerpt from the general principles. Note that the Declaration of Helsinki has been amended a few times over the years and this excerpt is from the most recent version, as amended in 2024. The full version can be found here.[33]

Also, see the Explainer Video here[34].

31. https://thedenverprinciples.com/
32. https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/
33. https://pdf-it.dev.acw.website/please-and-thank-you?url=https://www.wma.net/policies-post/wma-declaration-of-helsinki/&pdfName=wma-declaration-of-helsinki
34. https://www.youtube.com/watch?v=xc-Y9XqGL3Q

The Declaration of Helsinki

OFFICIAL OFFICIAL OFFICIAL OFFICIAL OFFICIAL

PREAMBLE

The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human participants, including the use of identifiable human material or data.

The Declaration is intended to be read as a whole, and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

While physicians adopt the Declaration, the WMA holds that these principles should be upheld by all individuals, teams, and organisations involved in medical research. These principles are fundamental to respecting and protecting all research participants, including patients and healthy volunteers.

GENERAL PRINCIPLES

1. The WMA Declaration of Geneva binds the physician with the words, "The health and well-being of my patient will be my first consideration," and the WMA International Code of Medical Ethics declares "The physician must commit to the primacy of patient health and well-being and must offer care in the patient's best interest."
2. The physician must promote and safeguard patients' health, well-being, and rights, including those involved in medical research. The physician's knowledge and conscience are dedicated to fulfilling this duty.
3. Medical progress is based on research that ultimately must include participants.
4. Even well-proven interventions should be evaluated continually through research for their safety, effectiveness, efficiency, accessibility, and quality.
5. Medical research involving human participants is subject to ethical standards that promote and ensure respect for all participants and protect their health and rights.
6. Since medical research occurs in the context of various structural inequities, researchers should carefully consider how the benefits, risks, and burdens are distributed.
7. Meaningful engagement with potential and enrolled participants and their communities should occur before, during, and following medical research. Researchers should enable potential and enrolled participants and their communities to share their priorities and values, participate in research design, implementation, and other relevant activities, and understand and disseminate results.
8. The primary purpose of medical research involving human participants is to generate knowledge to understand diseases' causes, development, and effects, improve preventive, diagnostic, and therapeutic interventions, and ultimately advance individual and public health.
9. These purposes can never precede individual research participants' rights and interests.
10. While new knowledge and interventions may be urgently needed during public health emergencies, upholding the ethical principles in this Declaration remains essential.
11. Physicians involved in medical research have a duty to protect the life, health, dignity, integrity, autonomy, privacy, and confidentiality of research participants' personal information. The responsibility for safeguarding research participants must always rest with physicians or other researchers and never with the participants, even though they have consented.
12. Physicians and other researchers must consider the ethical, legal and regulatory norms and standards for research involving human participants in the country or countries where the research originated and where it is to be performed, as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any protections for research participants outlined in this Declaration.
13. Medical research should be designed and conducted to avoid or minimise harm to the environment and strive for environmental sustainability.
14. Medical research involving human participants must be conducted only by individuals with the appropriate ethics, scientific education, training and qualifications. Such research requires the supervision of a competent and appropriately qualified physician or other researcher.
15. Scientific integrity is essential in the conduct of medical research involving human participants. Involved individuals, teams, and organisations must never engage in research misconduct.

Adopted by the 75th WMA General Assembly, Helsinki, Finland, October 2024[3]

INTERNAL USE ONLY

Nazi Experiments During WW2

THE EXCERPT BELOW IS FROM THE HOLOCAUST ENCYCLOPAEDIA, 2006, WASHINGTON, USA.

During World War II, several German physicians conducted painful and often deadly experiments on thousands of prisoners without their permission. Considering the inhumane conditions, lack of consent, and questionable research standards, modern scientists overwhelmingly reject the use of results from experiments in the camps.

EXPERIMENTS DEALING WITH THE SURVIVAL OF MILITARY PERSONNEL

Many experiments in the camps were intended to facilitate the survival of Axis[35] military personnel in the field. For example, at Dachau[36], physicians from the German air force and the German Experimental Institution for Aviation conducted high-altitude experiments on prisoners to determine the maximum altitude from which crews of damaged aircraft could parachute to safety. Scientists there also carried out so-called freezing experiments on prisoners to find an effective treatment for hypothermia. Prisoners were also used to test various methods of making seawater drinkable.

EXPERIMENTS TO TEST DRUGS AND TREATMENTS

At the German concentration camps, scientists used camp inmates to test immunisation compounds and antibodies for the prevention and treatment of contagious diseases, including malaria, typhus, tuberculosis, typhoid fever, yellow fever, and infectious hepatitis.

Ravensbrück's physicians conducted bone-grafting experiments and tested newly developed sulfa (sulfanilamide) drugs. At Natzweiler and Sachsenhausen, prisoners were exposed to phosgene and mustard gas to test possible antidotes.

EXPERIMENTS TO ADVANCE NAZI RACIAL AND IDEOLOGICAL GOALS

The most infamous were the experiments of Josef Mengele[37] on twins of all ages at Auschwitz. He also directed experiments, as did Werner Fischer at Sachsenhausen, to determine how different 'races' withstood various contagious diseases.

The research of August Hirt at Strasbourg University also intended to establish "Jewish racial inferiority". Additional gruesome experiments meant to further Nazi racial goals included a series of sterilisation experiments, undertaken primarily at Auschwitz and Ravensbrück. Scientists tested several methods to develop an efficient and inexpensive procedure for mass sterilisation.

INTERNAL USE ONLY

The Tuskegee Syphilis Study[38]

The US Public Health Service (USPHS) Syphilis Study at Tuskegee was a 40-year observational study that tracked the natural progression of untreated syphilis among 399 African American men in Macon County, Alabama. These men were not informed of their diagnosis and were misled to believe they were receiving free government healthcare. Crucially, no informed consent was obtained, and even after penicillin became the accepted treatment in the 1940s, it was deliberately withheld from the participants.

Despite awareness among some institutions, including the Macon County Health Department and Tuskegee Institute, the study continued until public outrage and ethical scrutiny led to its termination. In 1974, surviving participants and heirs received compensation through an out-of-court settlement. That same year, the National Research Act established the National Commission for the Protection of Human Subjects, which laid the groundwork for modern research ethics. This resulted in informed consent requirements and the institutionalisation of Institutional Review Boards (IRBs) to oversee human research protocols.

The Belmont Report (1979) further established core ethical principles: respect for persons, beneficence, and justice. By 1991, 16 federal agencies adopted the Federal Policy for the Protection of Human Subjects, reinforcing consistent, legally binding protections.

35. https://encyclopedia.ushmm.org/narrative/3343/en
36. https://encyclopedia.ushmm.org/narrative/4391/en
37. https://encyclopedia.ushmm.org/narrative/135/en
38. https://www.archives.gov/atlanta/highlights/tuskegee

Tenofovir PrEP Trials Controversy (2004-2006)[39]

Controversy emerged around trials testing tenofovir as HIV pre-exposure prophylaxis (PrEP) in Cambodia, Cameroon and Nigeria. At the 2004 International AIDS Conference in Bangkok, activists protested the Cambodian trial, citing poor HIV counselling, lack of medical care for participants who seroconverted, and limited community involvement in trial design. These ethical lapses sparked global concern, particularly regarding the unequal burden of risk borne by participants in low-resource settings.

In Cameroon in 2005, a trial led by Family Health International (FHI) was suspended after local and international criticism. A government-commissioned inquiry confirmed participants were not deliberately infected, but identified significant ethical and administrative shortcomings, such as understaffed counselling services and poor communication. Similarly, the Nigerian arm of the trial was voluntarily closed by FHI due to failure to meet operational and laboratory standards, threatening participant safety and data reliability.

Ethical debates centered on whether trials provided appropriate standards of care. Activists argued for treatment levels equivalent to those of high-income countries, while FHI maintained adherence to WHO guidelines. Critics also emphasised the need for both male and female condom distribution and comprehensive HIV risk education.

LESSONS AND ETHICAL IMPERATIVES FOR FUTURE RESEARCH

The Tenofovir trial controversies underscored the fragile relationship between researchers, participants and communities. Activists accused researchers of prioritising scientific data over participant rights, while researchers defended their compliance with local ethical standards and community consultations.

The situation highlighted the necessity of 'preventive diplomacy' – proactive engagement strategies to avoid ethical conflicts before they escalate. Suggested tools included:

- Early-warning systems (e.g. community liaison officers)
- Fact-finding missions to compare actual practice with protocols
- Inclusion of activist groups in community advisory boards
- Transparent media engagement
- Educational outreach on ethics, therapeutic misconception, and post-trial responsibilities

Following the trial disruptions, the Gates Foundation convened stakeholders in 2005 to clarify ethical expectations and promote better communication. This meeting emphasised the importance of genuine rather than tokenistic community involvement.

In sum, the failures of both the Tuskegee Study and the Tenofovir PrEP trials reveal persistent challenges in conducting ethical research, especially in marginalised or vulnerable populations. They collectively demonstrate that safeguarding human dignity in research requires sound scientific design and deep, ongoing ethical accountability to the people at its centre.

INTERNAL USE ONLY

39. https://pmc.ncbi.nlm.nih.gov/articles/PMC1176237/

Module 1

Fourteen Cases of HIV Cure, Post-Treatment, Elite and Exceptional-Elite Controllers

Scientists and researchers have presented two main pathways to an HIV Cure:

- **'Complete' or 'classic' cure** = complete elimination of the virus from the body, so no more virus remains anywhere – 7 patients, mostly cured by transplants to treat cancer

- **ART-free durable suppression (or control)** = the ability to control HIV growth in the body without HIV treatment such as ART – these are called post-treatment and/or elite controllers meaning that they have genetic mutations that prevent HIV replicating:
  - A cluster of patients in France, USA and Germany who received very early antiretrovirals before HIV replicated widely;
  - ii. Clusters of children in the USA and South Africa whose PMTCT-naïve early ART prevented transmission;
  - A panel of other patients whose genetic make-up seemingly prevents HIV from replication, such as the Buenos Aires and Barcelona patients; and
  - A number of other patients who have genetic mutations that control HIV.

- In total there are 14 different types of cases that have shown that HIV can be cured.

INTERNAL USE ONLY

Module 2

Research Ethics Guidelines

In response to the concerns raised in the 2004-6 early PrEP Trials, UNAIDS and AVAC produced the 2011 Good Participatory Practice Guidelines (UNAIDS/AVAC)[40]. These guidelines provide for 16 activities from the early stages of clinical trials to their end, designed to ensure effective community participation. Advocates insist that the mechanism of a GPP Plan for each trial be adapted to the trial's risks and benefits, and considered at the protocol approval phase; however, this is uneven across the clinical trials landscape.

The Council for International Organisations of Medical Sciences (CIOMS) was established jointly by the WHO and UNESCO in 1949. Their Guidelines41 relate mainly to the ethical justification and scientific validity of research; ethical review; informed consent; vulnerability of individuals, groups, communities and populations; women as research subjects; equity regarding burdens and benefits; choice of control in clinical trials; confidentiality; compensation for injury; strengthening of national or local capacity for ethical review; and the obligations of sponsors to provide healthcare services.

The European Code of Conduct for Research Integrity[42] provides for four ethical principles: (a) Reliability in ensuring the quality of research, reflected in the design, methodology, analysis and use of resources; (b) Honesty in developing, undertaking, reviewing, reporting and communicating research in a transparent, fair, complete and unbiased way; (c) Respect for colleagues, research participants, research subjects, society, ecosystems, cultural heritage and the environment; and (d) Accountability for the research from idea to publication, for its management and organisation, for training, supervision, and mentoring, and for its broader societal impacts.

INTERNAL USE ONLY

Homework Assignment

Ethics Checklist for an HIV Cure Trial

Re-read the Ethics guidelines. Create an ethics checklist for a cure discovery trial in your country using the following:

1. Criteria for a clinical trial's Good Participatory Practice Plan are found in the UNAIDS/AVAC GPP Guidelines
2. What legal options can enforce ethical practices identified in the SCIOMS Guidelines?
3. Describe conditions for product licensing in the European Union and specific country-level guidelines that apply to your context.

40. https://avac.org/project/good-participatory-practice/
41. https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf
42. https://allea.org/code-of-conduct/

Module 3

Key Terms in HIV Persistence

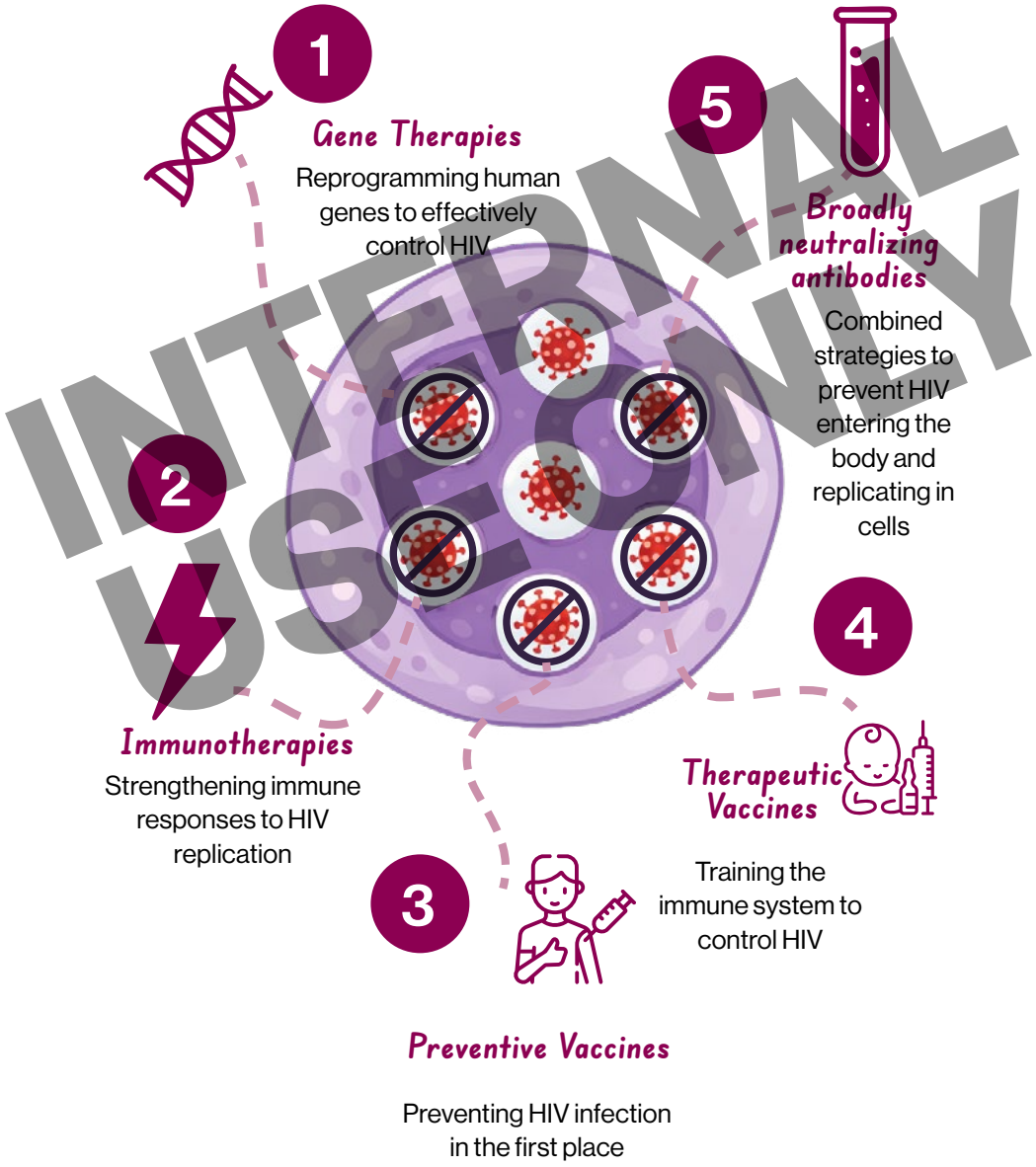
1. **Latent Reservoir** – A hidden 'storage place' in certain immune cells where HIV hides quietly without making new virus. This is why HIV comes back if treatment stops.
2. **Viral Reservoir** – Any place in the body where HIV can hide, not just in blood but also in the gut, brain, or lymph nodes.
3. **Integration** – The step where HIV slips its instructions (DNA) into a person's cells, becoming part of them.
4. **Proviral DNA** – The 'copy' of HIV's code that sits inside a person's DNA. Some copies are broken and harmless, but others can still make new viruses.
5. **Shock and Kill** – A cure idea: wake up ('shock') the hidden HIV, then get rid of those infected cells ('kill') so they can't spread virus again.
6. **Block and Lock** – Another cure idea: instead of waking HIV up, keep it permanently 'locked away' and unable to restart.
7. **Immune Checkpoint Inhibitors** – Medicines that 'take the brakes off' the immune system, helping it fight HIV-infected cells more strongly.
8. **Broadly Neutralising Antibodies (bNAbs)** – Super-antibodies that can block many different types of HIV, unlike normal antibodies that usually work on just one type.
9. **Analytical Treatment Interruption (ATI)** – A carefully supervised break from HIV medicines in a research study, used to test if a new approach can keep HIV under control.
10. **Functional Cure (Remission)** – HIV is still in the body, but the virus count is kept so low without medicine that it doesn't make someone sick or spread easily.
11. **HIV Viral Load (HIV RNA Copies)** – The amount of HIV in a person's blood is measured in copies of its genetic material (RNA).
12. **HIV Reservoir** – Hidden pockets of the virus that remain in specific body cells, even when HIV treatment is working well.
13. **Antiretroviral Therapy (ART)** – Medications that stop HIV from making more virus in the body, to help people stay healthy.
14. **Undetectable** – When HIV levels in the blood are so low that standard tests can't find them.
15. **Latent Form** – HIV's 'sleeping' form, a term used when it hides in cells without making new virus.
16. **CD4+ T Cells** – Key immune cells that HIV infects and uses to spread in the body.
17. **HIV Integration** – The process by which HIV inserts its genetic material into the DNA of human cells, making it a permanent part of the cell.
18. **Reverse Transcription** – The step in which HIV turns its RNA into DNA to insert it into human cells.
19. **Homeostatic Proliferation** – The process in which immune cells, including those infected by HIV, multiply to maintain balance in the immune system.
20. **Integration Site-Driven** – The location where HIV integrates into a cell's DNA affects how the virus behaves.
21. **Homeostatic** – Refers to maintaining balance in the body, for example keeping the immune system stable.
22. **Antigen-Driven** – Immune responses are caused by antigens, which are signals from foreign invaders such as viruses.
23. **Lymph Nodes and GALT** – There are areas in the body, such as lymph nodes and gut-associated lymphoid tissue (GALT), where immune responses occur and HIV can hide.
24. **Monocytes** – Immune cells in the blood that help fight infections and can carry HIV to other parts of the body.
25. **Macrophages** – Immune cells that 'eat' invaders like bacteria can also harbour HIV.
26. **Dendritic Cells** – Immune cells that alert the immune system to threats and can be infected by HIV.
27. **HIV DNA** – HIV's genetic material is converted from RNA to DNA and inserted into human cells.
28. **Quantitative Virus Outgrowth Assay (QVOA)** – A test that measures how much hidden HIV can be awakened from infected cells.
29. **Intact Proviral DNA Assay (IPDA)** – A test that counts HIV DNA copies in cells to measure the amount of virus that could still replicate.

INTERNAL USE ONLY

Module 3

Pathways To an HIV Cure

Curing HIV may require combining several strategies



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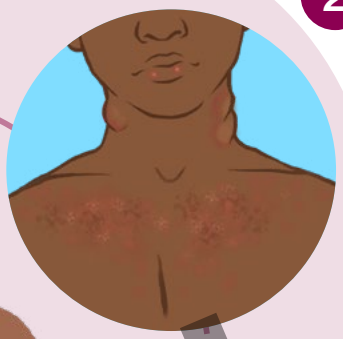
The process of HIV infection & persistence

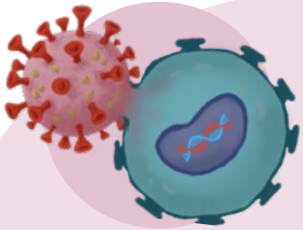
When HIV enters the human body, its goal is to hijack healthy immune cells and use their genetic blueprint to make more virus. HIV carries its genetic information in an acid called RNA (ribonucleic acid). Because human cells use another acid called DNA (deoxyribonucleic acid) as their genetic blueprint, HIV must first convert its RNA into DNA. When HIV enters a CD4 immune cell, it uses an enzyme it carries called reverse transcriptase to make this new DNA. The viral DNA then becomes part of the host cell's DNA, causing the cell to unknowingly produce new HIV that can infect other cells.

1

Two weeks after the HIV first enters the body, many viral cells have been copied and symptoms start showing as mout hulcers, swollen glands and rashes - the are signs that the immune system is fighting the virus and its goal to rapidly make copies of

2



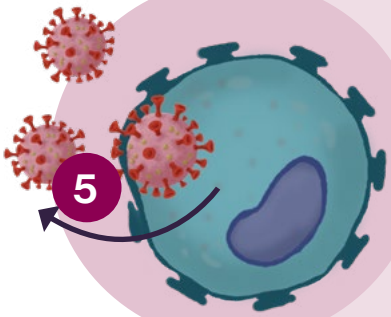


3



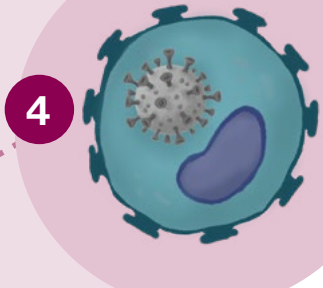
ART stops HIV enter, hijacking and replication

INTERNAL USE ONLY



5

To evade detection, HIV can remain hidden inside some infected immune cells in a "sleeping" (dormant) state. In this state, the viral DNA stays inside the cell's DNA without making new virus. Because antiretroviral therapy (ART) only stops HIV from making new copies of itself, these sleeping infected cells can remain in the body. If ART stops or the resting cells become active again, the virus can "wake up," start making new copies of itself, and infect other cells.



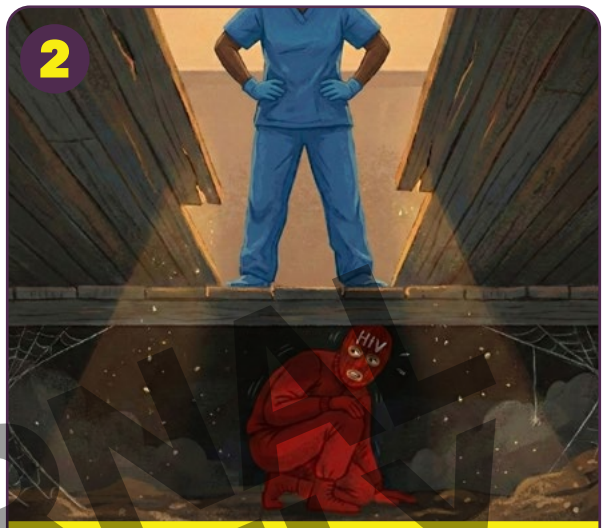
4

Stopping ART lets the virus re-enter, resume hijacking and replication

How close are we to finding a cure for HIV?



Think of your body as a big, beautiful house. One day, an intruder – HIV – breaks in. At first, you notice signs: broken windows, noise, maybe even damage. You feel sick. So, you call the security team; this is your antiretroviral therapy, or ART. They come in quickly, and lock down the rooms where the intruder was seen.



But this is not an ordinary intruder. HIV is clever. It knows how to hide in crawl spaces, behind walls and under floorboards – places no one checks. It does not leave. It just hides, staying quiet for years, not causing problems, but never really gone.



ART is powerful. It keeps the intruder from moving around or causing trouble, so you can live your life. But if you stop treatment, the intruder will come back and create chaos all over again.



This is why curing HIV is so hard. It's not just about stopping the intruder; it's about finding every secret hiding place, even the ones that seem empty. That's what scientists mean when they talk about the 'latent reservoir' – the hidden spots where HIV stays silent, waiting.

INTERNAL USE ONLY

Module 3

Why Is It So Hard to Cure HIV?

To understand why HIV Cure trials are still ongoing, we first need to look at how HIV hides in the body and why this makes it difficult to cure.

HIV hides even when you feel well

- HIV doesn't leave the body, even when someone is on treatment and feeling healthy.
- The virus hides in certain places called **reservoirs** – parts of the body where it 'sleeps' and cannot be reached by medicine.
- These hidden viruses are **inactive**, or 'silent', and the immune system doesn't even know they're there.

How does HIV become hidden?

- When HIV enters a person's immune cells (**CD4+ T-cells**), it changes its RNA into DNA and inserts it into the cell's DNA.
- If that cell goes into a resting state – meaning it's inactive – the virus also goes quiet.
- This is called **latency**, and it's like HIV has gone into hiding.

Why Is This a Problem?

- Antiretroviral treatment (ART) can **stop HIV from spreading**, keep the virus levels low, and prevent sickness.
- However, ART **cannot reach** or **remove** the silent virus hiding in resting cells.
- If someone stops taking their medicine, the virus wakes up and starts spreading again.

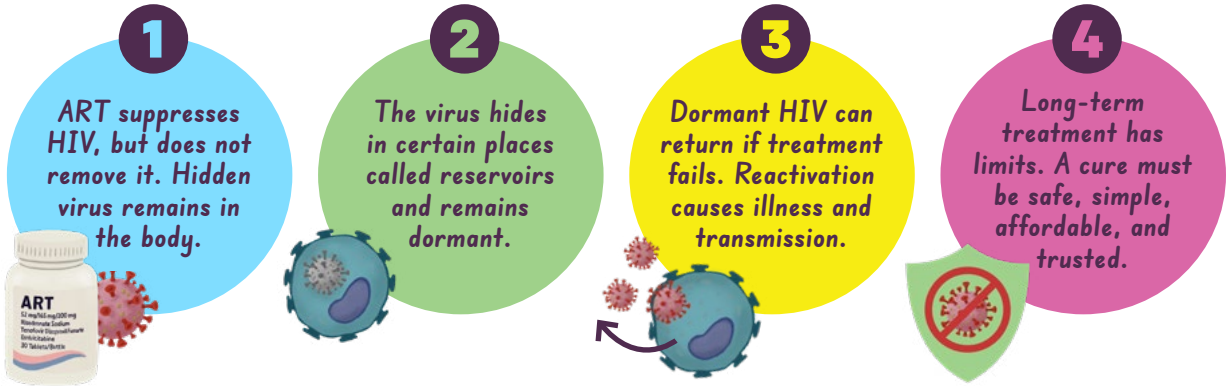
How ART works – step by step

- HIV attaches to a CD4 cell using special proteins (like **gp120**).
- It fuses with the cell using another protein (**gp41**) and enters.
- It uses an enzyme (**reverse transcriptase**) to turn its RNA into DNA.
- This HIV DNA is then inserted into the cell's DNA using an integrase enzyme.
- HIV can now either **stay quiet** (latent) or **become active**.
- If active, the virus makes more copies of itself, builds new virus particles, and releases them to infect other cells. A third enzyme, **protease**, helps new viruses mature.

Current ARV drugs **block many of these steps, but can't remove the silent virus** already hiding inside human cells' DNA.

What Scientists Are Trying to Do

- Cure research focuses on **finding ways to locate and remove the hidden virus**.
- This is one of the **biggest challenges** in HIV science today.
- Learning more about these hidden viruses – **where they are, how they work, and how to target them** – is key to finding a cure.



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Module 3

HIV Cure Research Studies

The HIV cure landscape has many different approaches to help people with HIV live healthy lives.
First, there is cART (combination antiretroviral therapy). This treatment uses medicines to stop HIV from growing in the body. It does not cure HIV, but helps people stay healthy and prevents them from spreading the virus to others (UNAIDS, 2020).
Next, Long-acting ART is a new medicine that lasts longer in the body. People can take it less often, such as once a month. This makes treatment easier and more convenient (Johnson **et al.,** 2021).
ART does not cure HIV completely. But the forms of ART listed below are what scientists are currently researching.
Broadly Neutralising Antibodies are special medicines made from natural immune proteins that can target many types of HIV. These antibodies can help stop the virus from multiplying, and are being studied as a possible cure or prevention tool (Baum **et al.,** 2018).
The first-generation HIV cures aim to remove all HIV from the body. They include methods such as stem cell transplants and other advanced treatments. One example is the 'Berlin patient', who was cured after a stem cell transplant (Hütter **et al.,** 2009).
The second-generation HIV cures focus on gene editing and immune system improvements. Techniques like CRISPR are used to try to erase HIV DNA or strengthen the body's ability to fight the virus (Liu **et al.,** 2019). These methods are currently being trialled in 2025/6, and are even sharing positive early results.
The third-generation HIV cures aim to combine treatments like ART, immune therapy and gene editing. They look for smarter ways to eliminate HIV completely and permanently from the body (Marcus **et al.,** 2022).
In summary, the HIV cure journey includes better medicines, new technologies, and innovative strategies to end HIV as a health problem.
It is believed an actual HIV Cure may possibly come from third-generation strategies in which people with HIV use a combination of treatments and therapies, possibly including genetic editing. What is most important is that this eventuality must be part of community and African leadership to safeguard community interests and produce a cure that is acceptable, affordable and accessible to all people living with HIV.

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The first-generation HIV cures aim to remove all HIV from the body.



The second-generation HIV cures focus on gene editing and immune system improvements.



The third-generation HIV cures aim to combine treatments like ART, immune therapy and gene editing.

Module 4

Key terms in HIV Cure Clinical Studies

1. **Analytical Treatment Interruption (ATI):** Temporarily stopping ART in trials to study the effects of experimental cure strategies.
2. **Block and Lock:** A method that keeps HIV permanently dormant in infected cells, preventing it from becoming active.
3. **Broadly Neutralising Antibodies (bNAbs):** Specialised antibodies that block many HIV strains from infecting cells.
4. **CAR-T Cells:** Genetically modified immune cells designed to better recognise and destroy HIV-infected cells.
5. **Combination Therapy:** Using multiple treatments together to target HIV at different stages or through different mechanisms.
6. **CRISPR-Cas9:** A gene-editing tool used to cut or modify parts of HIV DNA in infected cells.
7. **Functional Cure:** Controlling HIV without the need for ongoing ART, though the virus remains in the body.
8. **Gene Therapy:** Techniques to modify or repair genes to eliminate HIV or make cells resistant to infection.
9. **Immune Modulators:** Substances that boost the immune system's ability to fight HIV, especially after reactivation.
10. **Immunotherapy:** Treatments that enhance the immune system's natural defences to fight HIV.
11. **Informed Consent:** Ensuring participants fully understand the risks and benefits before joining a clinical trial.
12. **Integrase Inhibitors:** Drugs that block HIV from inserting its DNA into human cells.
13. **Latency-Reversing Agents (LRAs):** Drugs that 'wake up' hidden HIV in reservoirs to make it targetable.
14. **Protease Inhibitors:** Drugs that stop HIV from maturing into infectious particles.
15. **Shock and Kill:** A strategy to reactivate dormant HIV ('shock') and eliminate it ('kill').
16. **Stem Cell Transplants:** Replacing immune cells with donor cells resistant to HIV infection.
17. **Sterilising Cure:** Completely removing all traces of HIV from the body.
18. **T-Cell Therapies:** Using immune cells to target and destroy HIV-infected cells.
19. **Therapeutic Vaccines:** Vaccines designed to help the immune system control HIV in people already infected.

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Module 4

History of HIV CURE Trials

The First HIV Medicine – AZT

In the 1980s, scientists were desperate to find a medicine for people dying from AIDS. They discovered a drug called AZT, which was first made to fight cancer, but didn't work for that. AZT helped reduce deaths and sickness caused by HIV, though it had strong side effects. In 1987, it became the first approved HIV treatment. It worked by stopping HIV from making copies of itself.

Over time, researchers found that lower doses of AZT worked better, with fewer side effects. They also learned AZT could help people before they became very sick with AIDS.

Why One Drug Wasn't Enough

HIV changes quickly in the body. If only one drug is used, the virus can learn to resist it. This means the drug will stop working. Many people on AZT alone developed resistance within days.

So, scientists began to combine two drugs. In the early 1990s, AZT with another medicine called ddC worked better than AZT alone. By 1995, studies confirmed that two-drug combinations slowed the illness more effectively than one drug.

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Big Progress: Three-Drug Therapy (HAART)

In 1996, a significant breakthrough occurred. Scientists introduced a three-drug treatment, **HAART (Highly Active Antiretroviral Therapy)**. It combined different types of HIV medicines, including a new group called **protease inhibitors**.

Triple therapy could lower the amount of HIV in the blood so much that tests couldn't find it. But it was hard to take: many pills, every day, at different times, with or without food, and with substantial side effects.

New Types of HIV Drugs

New classes of medicines followed. In the mid-1990s, drugs called **NNRTIs** were easier to make and more affordable. Then, scientists found that HIV enters cells using special 'doors' like **CCR5 and CXCR4**. One new drug, **maraviroc**, blocks one of these doors.

In 2007, a new inhibitor, an example being **raltegravir, was introduced**. HIV can become resistant to these, but newer versions such as **dolutegravir (approved in 2013)** are stronger, work longer, and are easier to take. Dolutegravir is now a **preferred first-line treatment** globally because it works well and is safe and affordable.

Experimental Treatments: Broadly Neutralising Antibodies (bNAbs)

Today, scientists are exploring new ideas for a cure. One exciting area is **bNAbs** – special antibodies that block HIV by attacking its outer layer. These are being tested in trials and may one day help control HIV without daily pills. Some powerful bNAbs come from African research and are designed to work better for people on the continent.

OR

1980s

Emergence of HIV

- 1983: HIV was identified as the cause of AIDS by Dr. Luc Montagnier and Dr. Robert Gallo.
- 1987: FDA approves Zidovudine (AZT), the first drug for treating HIV. While effective, it has severe side effects.

1990s

Foundations of Modern Treatment

- 1994: The ACTG 076 trial demonstrates that Zidovudine can reduce mother-to-child transmission of HIV by 67%.
- 1995: FDA approves Saquinavir, the first protease inhibitor, marking the beginning of Highly Active Antiretroviral Therapy (HAART). HAART combines drugs to attack HIV at multiple stages.
- 1997: Introduction of combination therapy transforms HIV into a manageable chronic disease for many.

2000s

Functional Cure Research Begins

- 2007: The 'Berlin Patient' becomes the first person cured of HIV through a bone marrow transplant with CCR5 delta32 mutation cells, blocking HIV entry.
- 2009: Discovery of latency-reversing agents sparks research into activating and eliminating dormant HIV-infected cells.

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2010s

Broadening the Scope

- 2011: The HPTN 052 trial shows that ART reduces sexual transmission of HIV by 96%, reinforcing the concept of 'treatment as prevention'.
- 2013: The 'Mississippi Baby' case shows temporary remission after early ART, though the virus later reemerges.
- 2018: The introduction of broadly neutralising antibodies (bNAbs) to target diverse HIV strains shows promise in early trials.

2020s

Clinical Trials and Global Efforts

- 2020: FDA greenlights Phase 1 trials for AGT103-T, a gene therapy targeting HIV reservoirs.
- 2021: Trials with AGT103-T begin; early results show no severe side effects.
- 2023: Analytical treatment interruptions test long-term remission after AGT103-T therapy
- 2024: DELIVER initiative expands HIV remission research globally, focusing on community and scientific collaboration

2020s

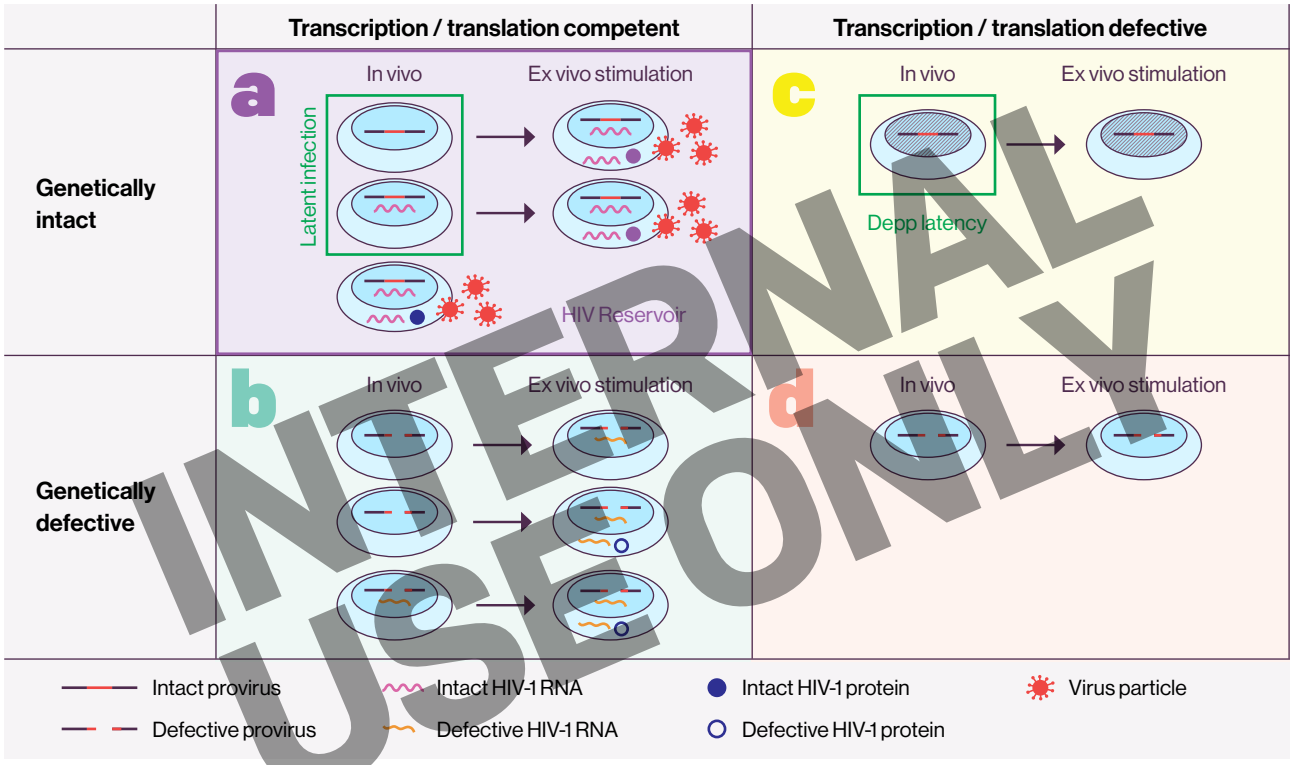
Vaccination Efforts

- 2009: RV144 trial in Thailand demonstrates a modest reduction in HIV acquisition (31% efficacy), providing a foundation for future vaccine development.
- 2024: Ongoing trials like N-803 in Thailand aim to reverse latency and strengthen immune responses.

Module 4

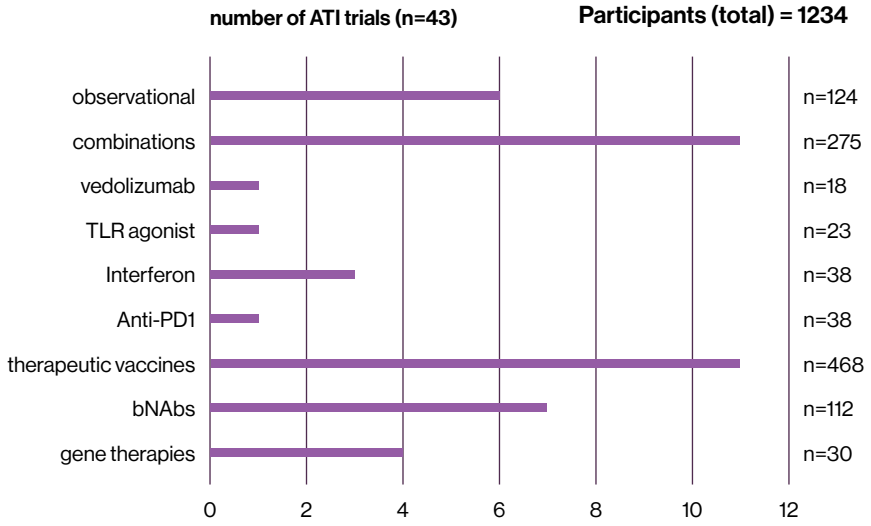
Analytical Treatment Interruptions

Notes on ATI for case study adapted from https://pmc.ncbi.nlm.nih.gov/articles/PMC8251690/[43]
Understanding Analytical Treatment Interruptions (ATI) in HIV Cure Trials
Analytical Treatment Interruption (ATI) is a research strategy used in HIV cure trials to temporarily stop antiretroviral therapy (ART) and observe how the body responds. It helps scientists evaluate new treatments designed to control HIV without continuous medication.



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Current ATI cure trials



Primarily sites in USA
1 paediatric study
Majority set point

ATI in LMIC

- Botswana
- Puerto Rico
- Thailand

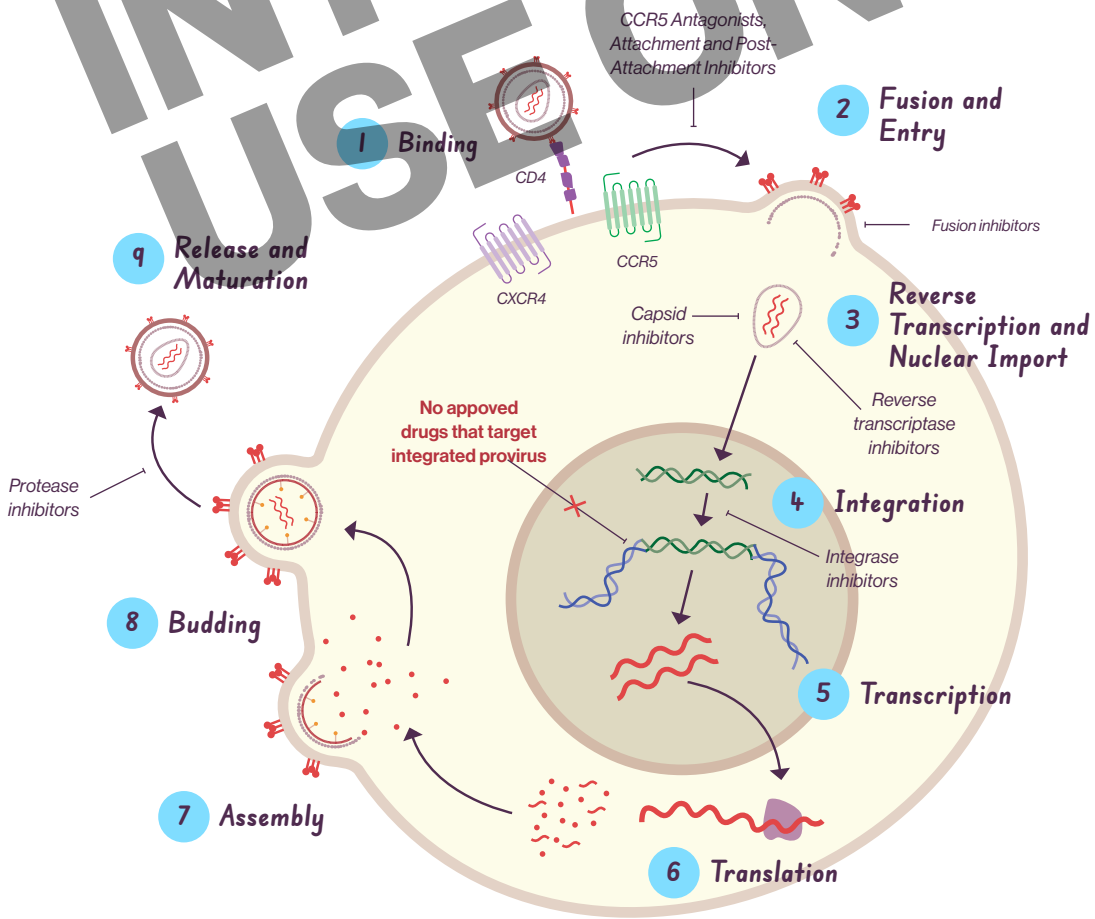
43. https://pmc.ncbi.nlm.nih.gov/articles/PMC8251690/

An analytical treatment interruption (ATI) is a temporary pause in using daily or long acting antiretrovirals



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Life cycle of HIV



Types of ATI Trials

1. ART Substitution Studies
    - These trials stop ART but continue other experimental treatments, such as broadly neutralising antibodies (bNAbs).
    - Example: Participants might receive bNAbs such as 3BNC117 and 10-1074 before stopping ART, then continue to receive these antibodies during the ATI phase.
    - Purpose: To test if the new treatments can delay the return of detectable HIV (viral rebound).

2. Full Discontinuation Studies
    - These trials stop all treatments, including ART and experimental therapies, after a 'washout' period to clear the body of investigational agents.
    - Purpose: To assess the ability of the immune system or other interventions to maintain viral suppression without any treatment.

Evolution of ATI Trials

- Early Trials (1990s-2000s):
    - Originally used to test therapeutic vaccines or reduce ART exposure.
    - Safety concerns arose after studies such as the 2006 SMART trial showed risk of prolonged treatment interruptions, for example increased illness and death rates.
- Modern Trials:
    - Shorter ATI phases with strict monitoring to minimise risks.
    - ART is restarted immediately if HIV levels in the blood exceed a specific threshold, ensuring participant safety.

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Key Features of Contemporary ATI Trials

- Shorter Duration: Minimises the time participants are off ART to reduce risks.
- Frequent Monitoring: Viral load (HIV level in the blood) is closely monitored to ensure safety.
- Outcome Measures:
    - Time to viral rebound: How long HIV stays undetectable after stopping treatment.
    - Viral control post-rebound: If the immune system can control HIV without medication.
    - Safety Protocols: ART is restarted promptly if the virus begins to increase significantly.

Why ATI Trials Are Important

ATI trials are a crucial part of HIV cure research because they allow scientists to:

- Test whether new treatments can control HIV without daily medication.
- Study how the virus behaves when ART is stopped.
- Explore strategies for achieving long-term remission or a functional cure.

Safety in ATI Trials

While early ATI trials raised safety concerns, modern approaches prioritise participant health with advanced designs and monitoring, making them a safer and more effective tool in the quest to cure HIV.

Module 5

Action Plan to introduce HIV Cure Strategies to a constituency

Community/Setting/Population: HIV Cure Introduction Plan

Activity	Duration	Estimated Cost
Outcome 1: What is the first change you want to see in the constituency you are working with ? • Does it have subpoints that build up to the specific result in Outcome 1? • xx		
List activity here starting with a verb	Start and end date	Estimated cost for the whole activity
(There can be more than one intermediate outcome, just duplicate this section to 3+) **Outcome 2: What is the next change you want to see in the constituency you are working with ?** • Does it have subpoints that build up to the specific result in Outcome 2? • xx		
List activity here starting with a verb	Start and end date	Estimated cost for the whole activity
Final Outcome: Collecting, sharing, analysing the evidence of the preceding activities • Specific evidence for named result 1? • Specific evidence for named result 2+? • Analysis of evidence • Community-led and stakeholder-shared interpretation of findings • Action plan for sustaining HIV Cure leadership in the community/population/constituency of focus		
Action 1	Start and end date	Estimated Cost
Action 2		
Action 3		

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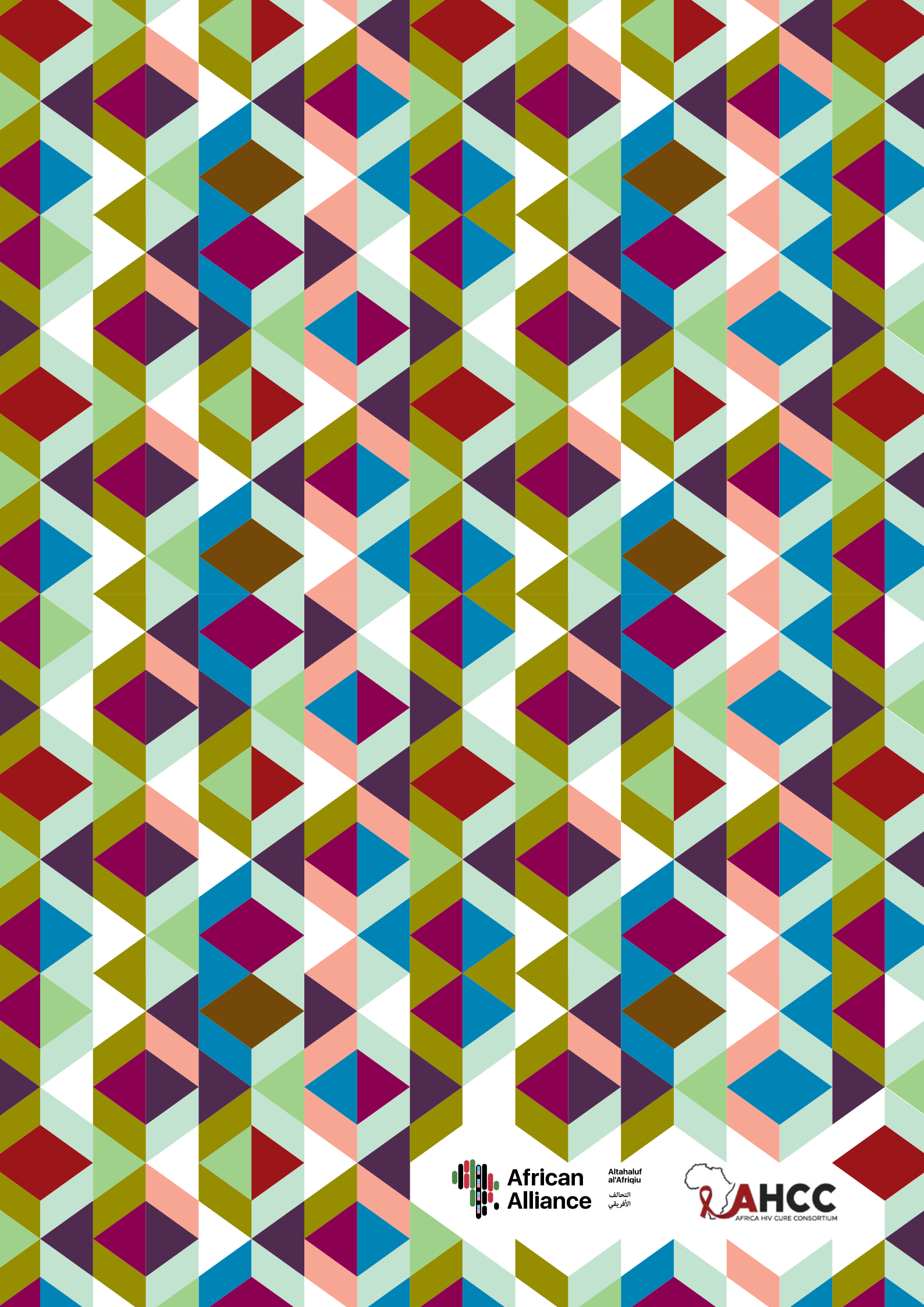
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