What We Know about HIVDR for New PrEP Methods

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10 SEPTEMBER 2024

2024 AFRICA REGIONAL PREP WORKSHOP

NAIROBI, KENYA

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MOSAIC

Maximizing Options to Advance Informed Choice for HIV Prevention

THE CATALYST STUDY

Outline

- Basics of INSTI Resistance
- INSTI Resistance Risk with PrEP
- CAB PrEP Resistance Monitoring in MOSAIC
- Looking ahead to Lenacapavir
- Closing Messages

Integrase Strand Transfer Inhibitors (INSTI)

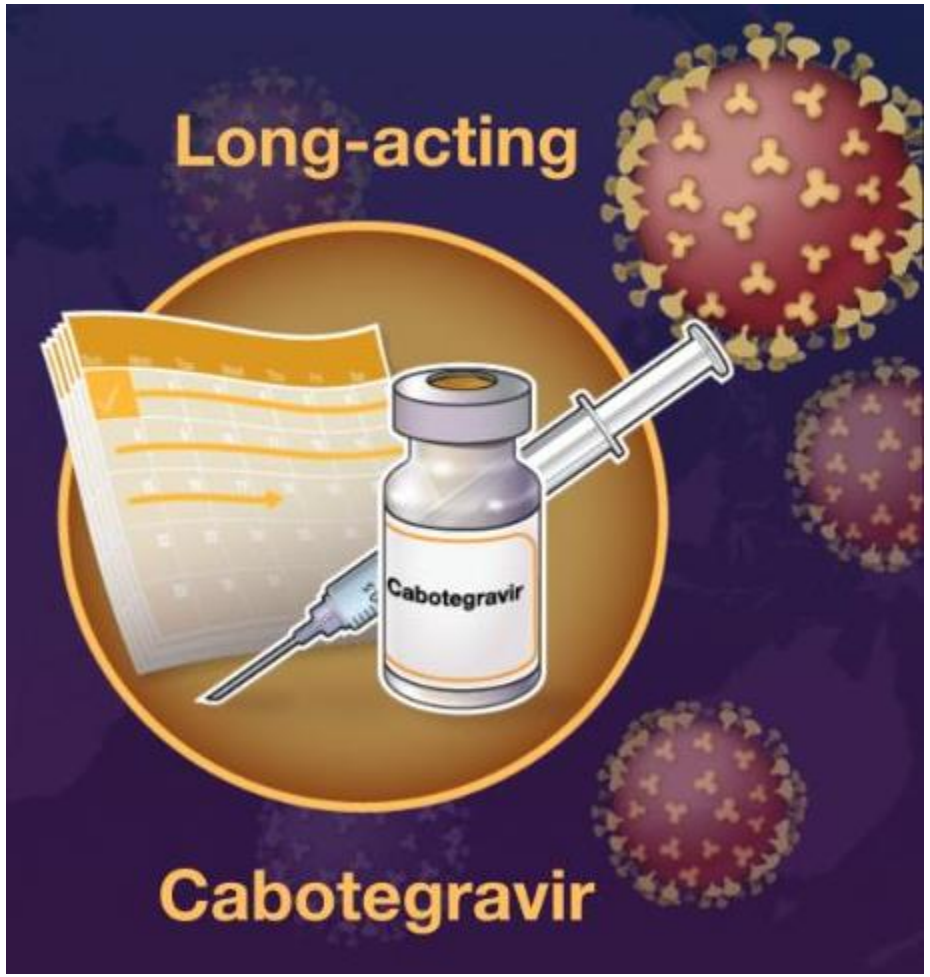


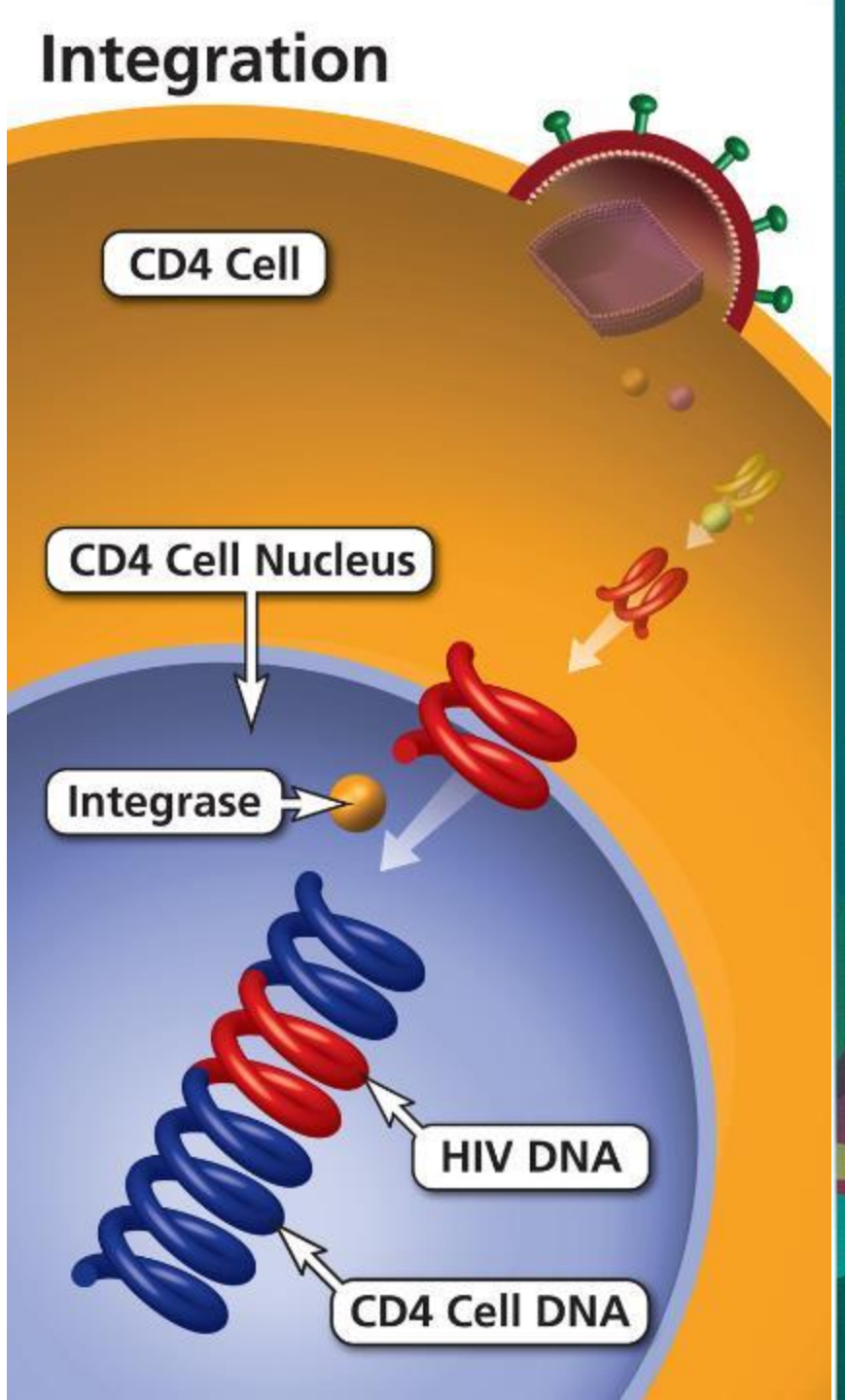
Image: https://www.nejm.org/do/10.1056/NEJMdo006117/full/

Used for Antiretroviral Therapy (ART)

- Bictegravir
- **Cabotegravir* – also used for PrEP**
- **Dolutegravir – 1st line ART**
- Elvitegravir
- Ralegravir

What HIV Integrase Does

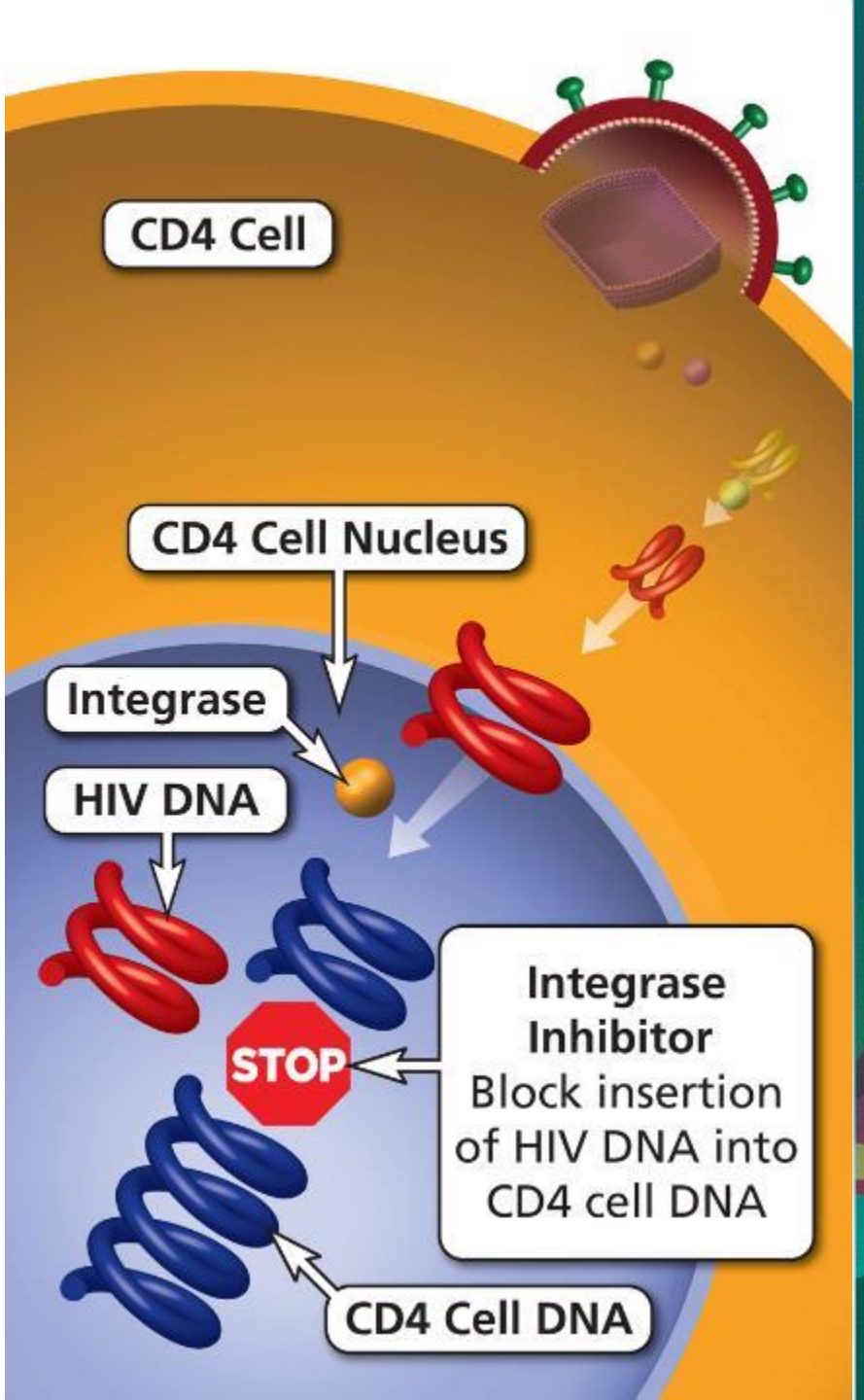
INTEGRASE (INT) is an HIV enzyme that allows **HIV DNA** to incorporate itself into the **HOST HUMAN GENOME.**



https://clinicalinfo.hiv.gov/en/glossary
https://retrovirology.biomedcentral.com/articles/10.1186/s12977-022-00608-1

How do INSTIs Work?

INTEGRASE STRAND TRANSFER INHIBITORS (INSTI)
block insertion of HIV DNA into cell DNA



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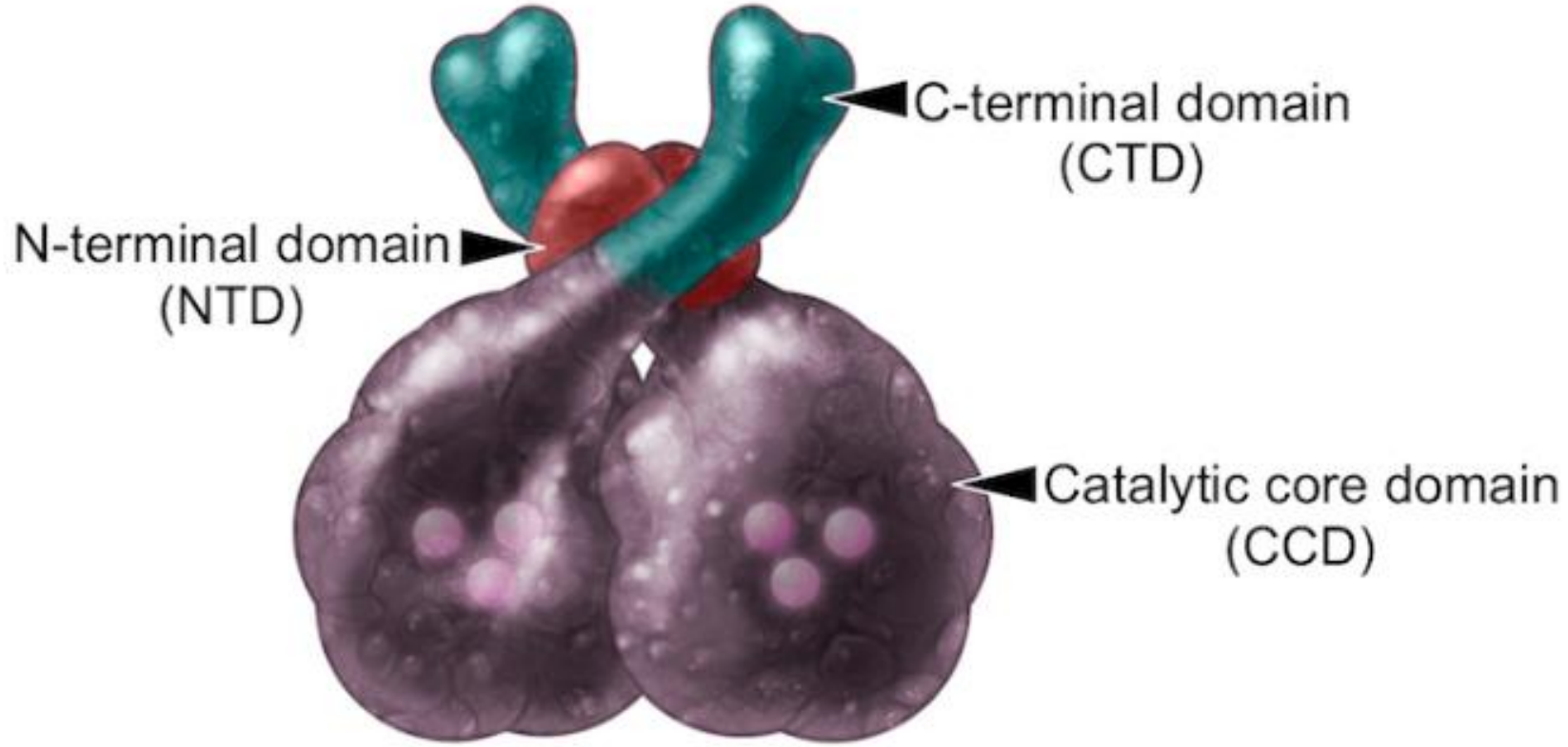
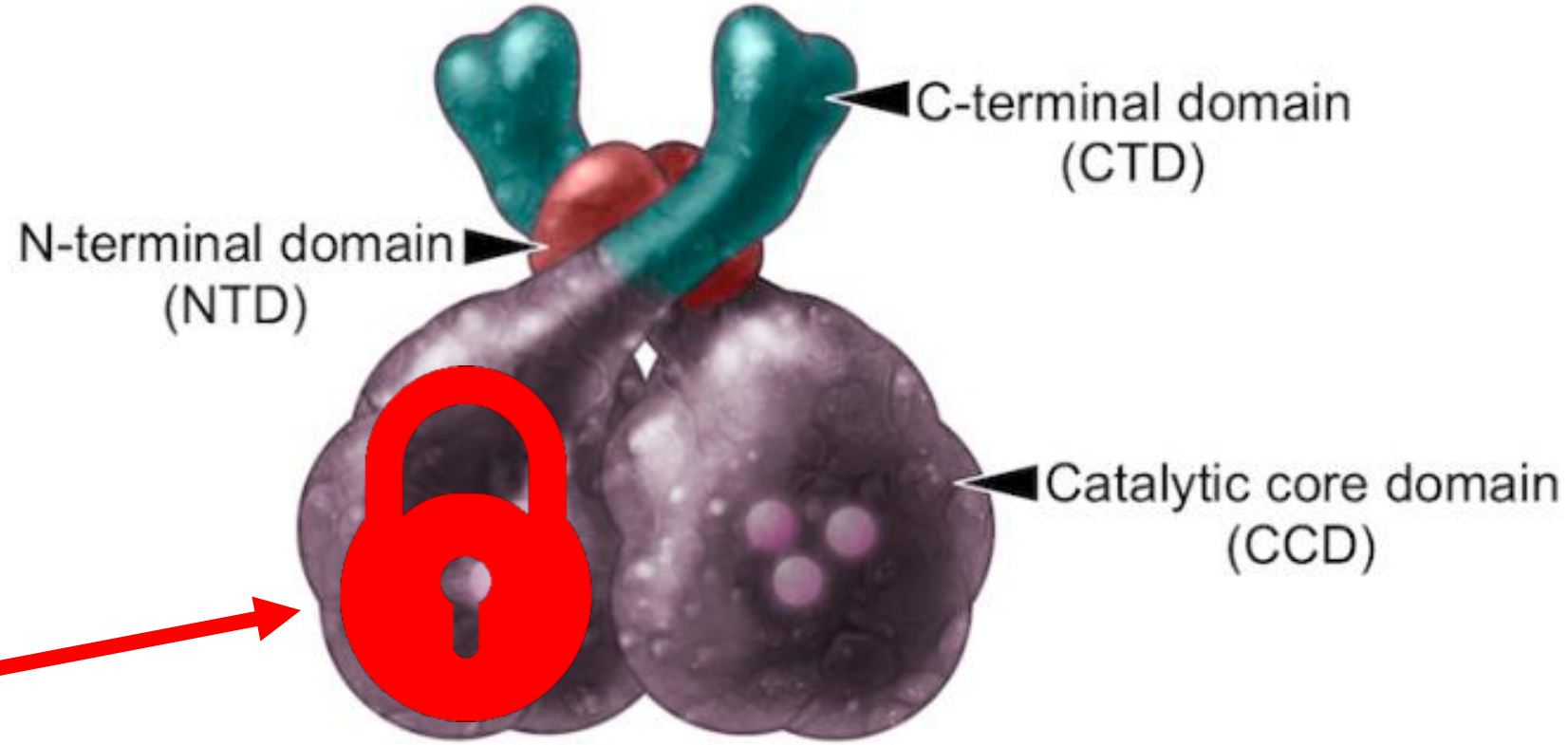
The integrase enzyme



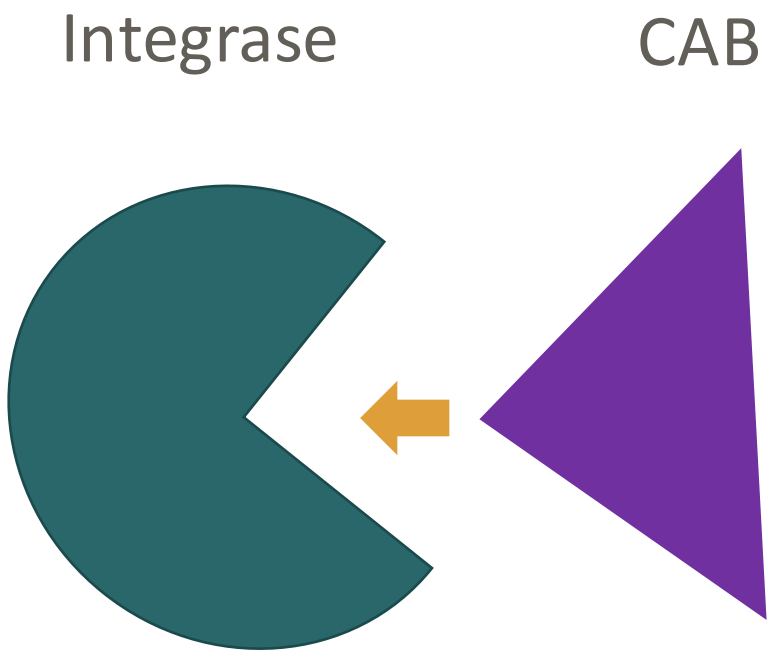
https://www.hiv.uw.edu/go/antiretroviral-therapy/evaluation-management-virologic-failure/core-concept/all

The integrase enzyme blocked by INSTI



https://www.hiv.uw.edu/go/antiretroviral-therapy/evaluation-management-virologic-failure/core-concept/all

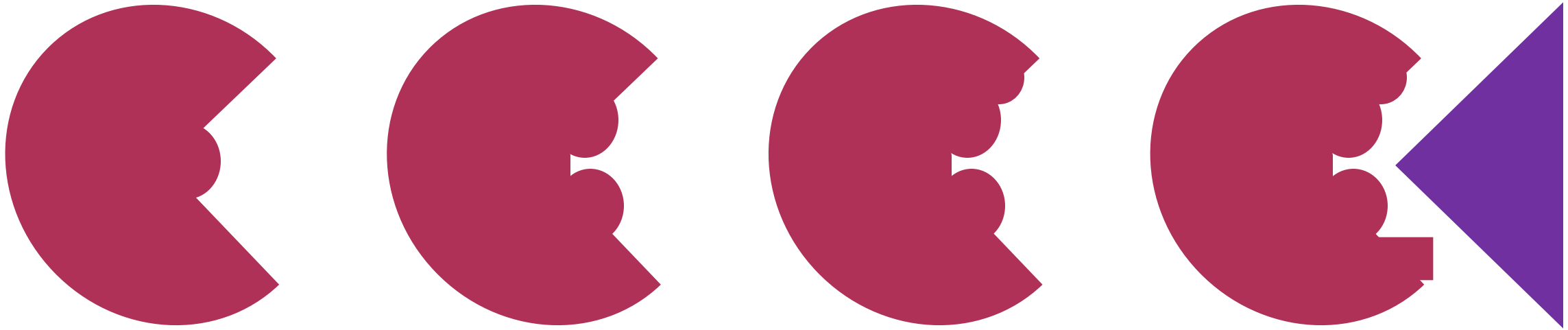
How does cabotegravir (CAB) work?



How does INSTI resistance happen?

CAB no longer “fits” allowing HIV to avoid it – **RESISTANCE!**

Mutations change the shape of integrase



Mutations can “accumulate”
The worse CAB “fits” the higher the resistance.

Risks to ART after Acquiring HIV on CAB PrEP

Number of INSTI Mutations	Level of INSTI Resistance
1 Mutation (e.g. G118R, Q148KR, R236K)	• Low (5-10-fold)
2-3 Mutations	• Moderate to high (>10-fold)
4 or more mutations	• High (>100-fold)

Parikh, Koss, Mellors. Curr HIV/AIDS Reports 2022

Risk of INSTI Resistance with CAB PrEP

"LEVI" Syndrome*

Delayed detection of HIV infection could lead to accumulation of mutations causing high-level INSTI resistance

Risk of HIV Drug Resistance with HIV infection on CAB-LA

Parikh, Koss, Mellors 2022

*Eshleman S et al. CROI 2023 #160

Delayed Seroconversion Observed in HPTN 083

HPTN 083 analysis in participants who acquired HIV[1]

	Recent CAB PrEP (<6 months) N = 18	No recent CAB PrEP (>6 months) N = 14
Delayed Seroconversion	14 (78%)	1 (7%)

Insufficient data in women – only 4 seroconversions on CAB in HPTN-083.[2]

1. Marzinke et al.. Antimicrob Agents Chemother 67(4): 20.
2. Delany-Moretlwe *et al. Lancet 2022* 23

Risk of INSTI Resistance with CAB PrEP

"LEVI" Syndrome*

CAB not protective against transmitted INSTI resistance from a partner

Delayed detection of HIV infection could lead to accumulation of mutations causing high-level INSTI resistance

Risk of HIV Drug Resistance with HIV infection on CAB-LA

Parikh, Koss, Mellors 2022

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Rates of Pre-Treatment INSTI Resistance are Low

Table 3. Pretreatment HIV drug resistance to DTG among adults initiating or reinitiating ART, 2016–2021

Country	Survey population	HIV drug resistance	
	n	%	95% CI
Argentina (2019)	375	0.0	0.0–1.0
Belize (2021)	66	0.0	0.0–5.5
El Salvador (2018)	197	0.0	0.0–1.9
Ethiopia (2017)	341	0.0	0.0–1.1
Guatemala (2016)	206	0.0	0.0–1.8
Mexico (2017)	1855	0.0	0.0–0.2
Nicaragua (2016)	166	0.0	0.0–2.3
Paraguay (2019)	208	0.0	0.0–1.8
South Sudan (2018)	256	0.2	0.0–1.2
Uruguay (2018)	205	0.0	0.0–1.8
Zambia (2019)	135	0.0	0.0–2.8

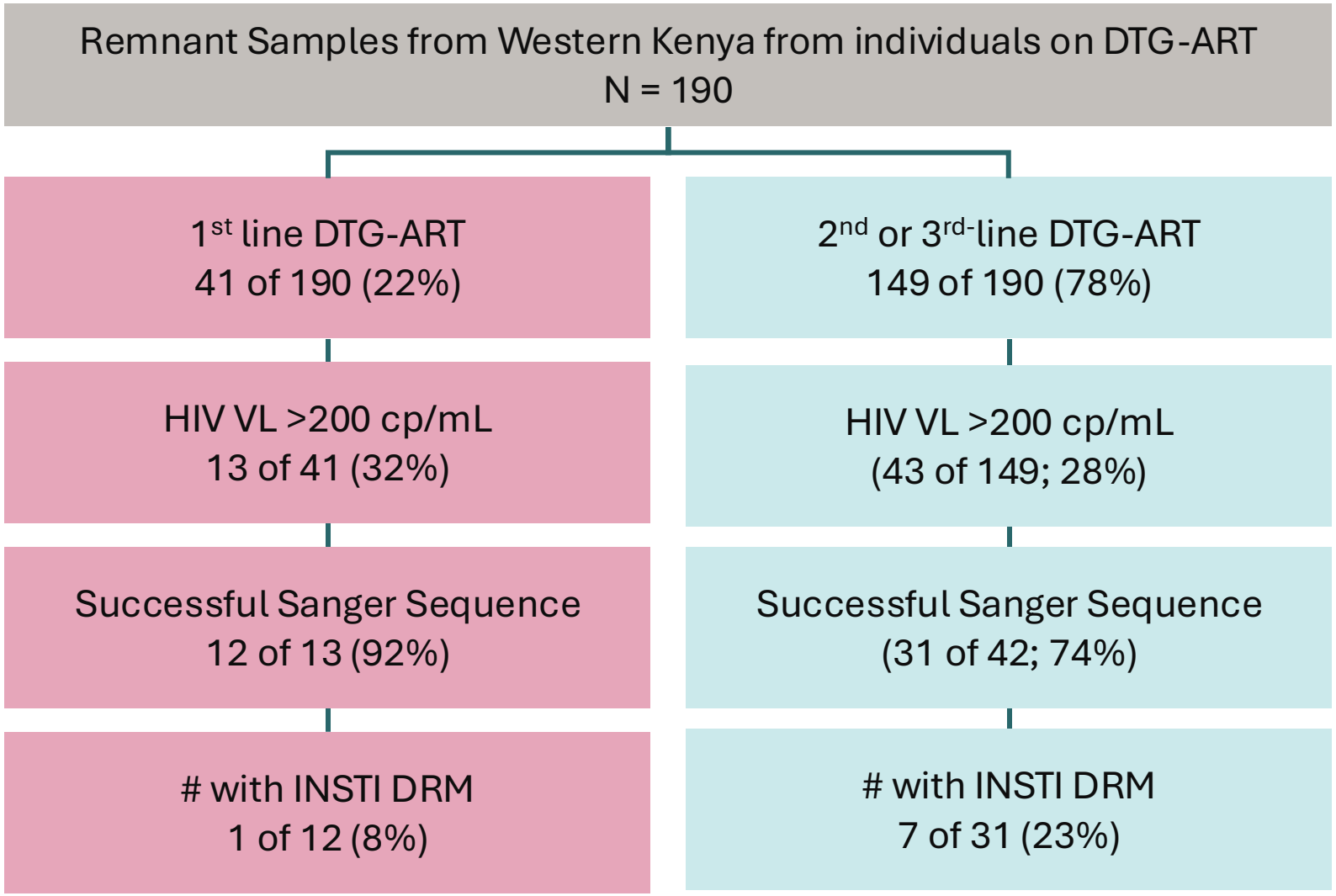
HIV drug resistance was defined as predicted resistance penalty score ≥15 using the Stanford HIVdb algorithm.

Limitations:

- 10/11 surveys conducted ≥5 years ago, when DTG use was less common
- Only 1 survey (Zambia) in Southern Africa
- Surveillance for INSTI not yet scaled up

2024 WHO HIVDR Brief Report
9789240086319-eng.pdf (who.int)

Resistance in ART-Experienced Individuals without Virologic Suppression on DTG: Kenya Study



Risk of developing DTG resistance with treatment may be higher in those with a background of pre-existing mutations.

Kingwara *et al.* CROI 2024. Poster #677

Risk of INSTI Resistance with CAB PrEP

"LEVI" Syndrome*

CAB not protective against transmitted INSTI resistance from a partner

Delayed detection of HIV infection could lead to accumulation of mutations causing high-level INSTI resistance

Acquiring HIV on CAB despite on-time injections

Risk of HIV Drug Resistance with HIV infection on CAB-LA

Parikh, Koss, Mellors 2022

*Eshleman S et al. CROI 2023 #160

HIV Infections in HPTN-083

- Number of seroconversions **low** (6 seroconversions in individuals with **on-time** injections)
- All 6 had INSTI resistance

Q146L, **Q148R, N155H, R263K**	**N155H,** S230R	**R263K**	M50I, **E138K, G140A, Q148R**	M50I, **R263K**	L74I, **Q148R**

Ref: Marzinke et al.. Antimicrob Agents Chemother 67(4): 2023

Low Numbers of Reported HIV Infections on CAB PrEP: Case Studies from the United States

Location	Case	PrEP History	CAB Levels	HIVDR
Illinois	28 yr NB	TAF/FTC (10 months) CAB (3 on-time)	High	Not performed
OPERA Cohort (United States)	Unknown	TAF/FTC (70 days) CAB (3 on-time)	Unknown	Unknown
California	23 yr NB	TAF/FTC (5 weeks) CAB (3 on-time, 4th delayed, 5th on-time; gap, then 2 on-time)*	High	Q148R, A128T (low-frequency)

*OPERA Cohort >40,000 PrEP Users in U.S. in routine care

**Took 7 days of TAF/FTC during delayed CAB dose; had a 6-month gap in care before re-starting CAB.

Hazra AIDS 2023; Mills CROI 2024 Poster 1109; Koss *et al.* OFID 2024

Importance of monitoring for HIV drug resistance with CAB PrEP

- To understand local rates of resistance in PrEP clients who seroconvert during oral PrEP or CAB LA use
- To ensure effectiveness of PrEP programs and to understand if additional support is needed for PrEP adherence and/ or routine HIV testing
- Ensure the ARVs used for both treatment and prevention remain effective

PrEP HIVDR Monitoring in MOSAIC

Implement research protocol to assess HIVDR in PrEP seroconverters

Kenya | Zimbabwe | Eswatini | Zambia | Lesotho

Planned

In planning:
Uganda
Namibia

Assess seroconversions in CATALYST for HIVDR

Kenya | Zimbabwe | Uganda | Lesotho | South Africa

Partner with existing PrEP Demo Projects to add HIVDR monitoring to their protocol or procedures

South Africa

Levy et al Glob Health Sci Pract. 2022; 10(2)

Research Gaps

Success of 1st-line DTG-based regimens:

- On individuals with INSTI resistance from PrEP?
  - 2nd-line regimens more expensive and harder to take
  - NNRTI-based regimens risky in regions with high rates of transmitted resistance

- **Study of treatment outcomes after AHI on CAB PrEP needed to inform choice of ART.**

MOSAIC HIVDR Monitoring Study

Frequency of HIVDR with HIV Acquisition on PrEP

ART Outcomes 6 and 12 months after acquiring HIV on PrEP (in planning stages)

HIV Diagnosis

- Blood Collection
- Clinical Records
- Viral load, HIVDR Test
- Storage for Future Testing

6-month visit

- Blood Collection
- Clinical Records
- Viral load, HIVDR Test
- Storage for Future Testing

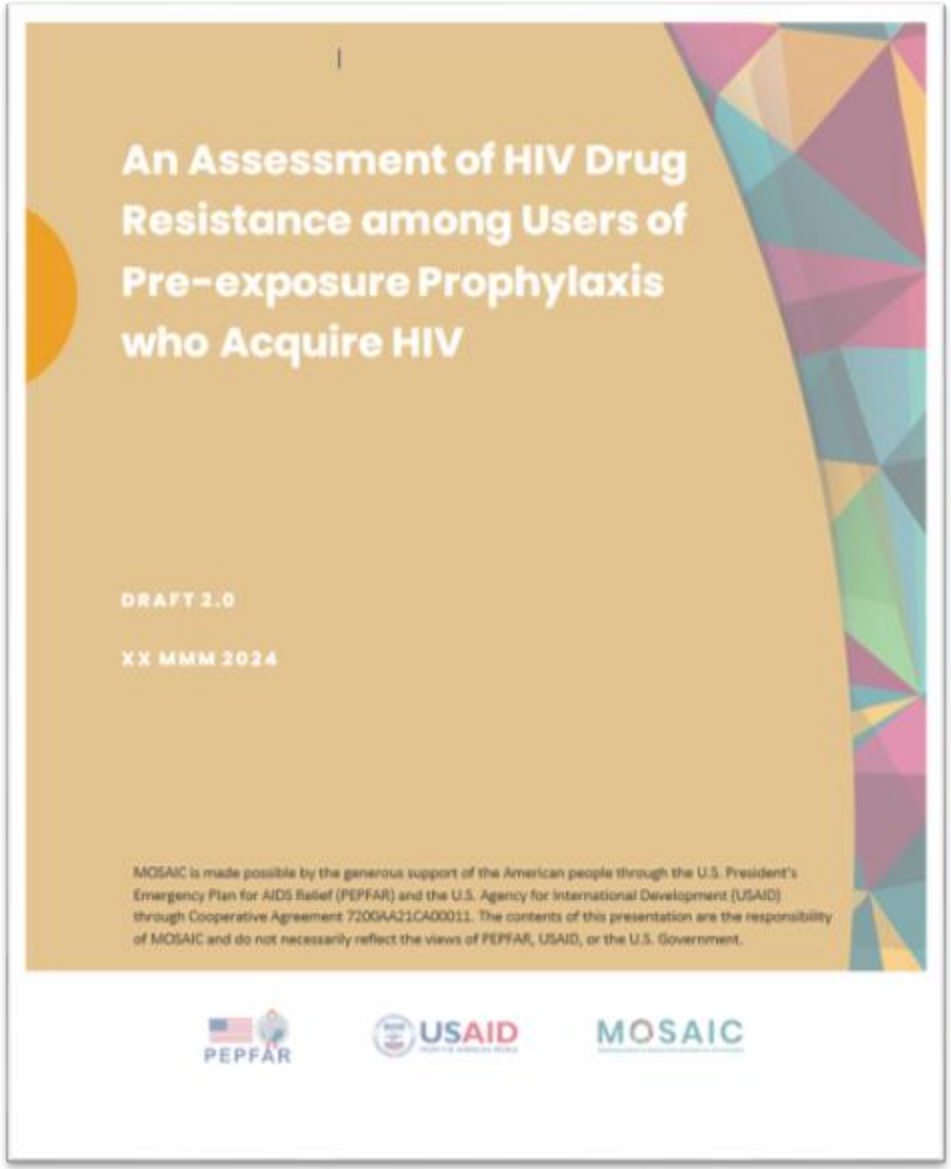
12-month visit

- Blood Collection
- Clinical Records
- Viral load, HIVDR Test
- Storage for Future Testing

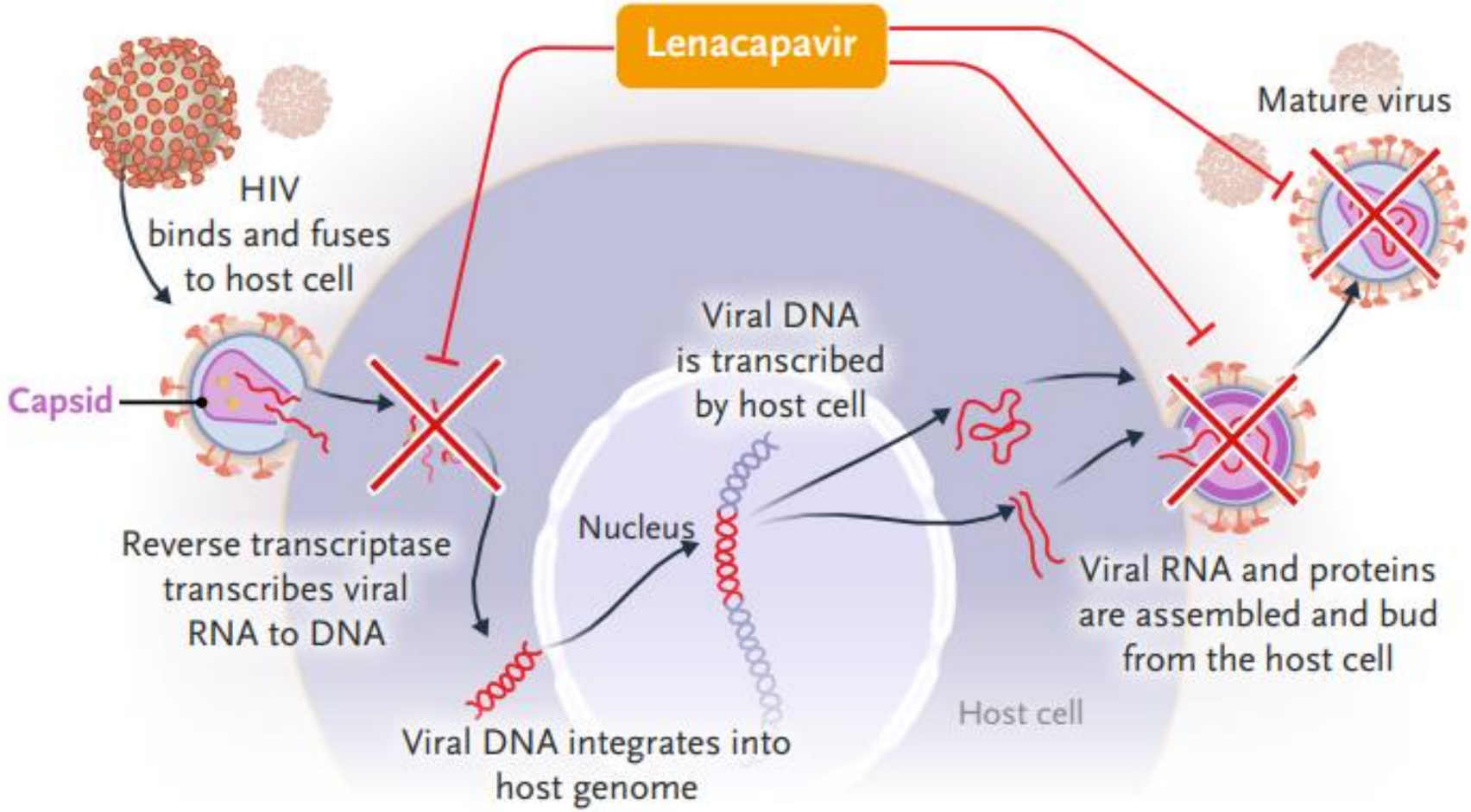
- MOSAIC kit and training provided to service delivery sites
- Future testing includes PK and sensitive resistance testing (for low copy samples) if needed

Study Objectives

- To assess the frequency of HIV-1 drug resistance mutations among PrEP clients who test HIV positive after initiating PrEP
- To assess the relationship between HIV drug resistance and PrEP adherence in individuals who test HIV positive on PrEP
- To characterize virologic suppression and HIV drug resistance at 6 and 12 months on ART, in individuals using PrEP who acquired HIV



Lenacapavir (LEN) – How it works



Segal-Maurer S et al. DOI: 10.1056/NEJMoa2115542

Resistance to Lenacapavir

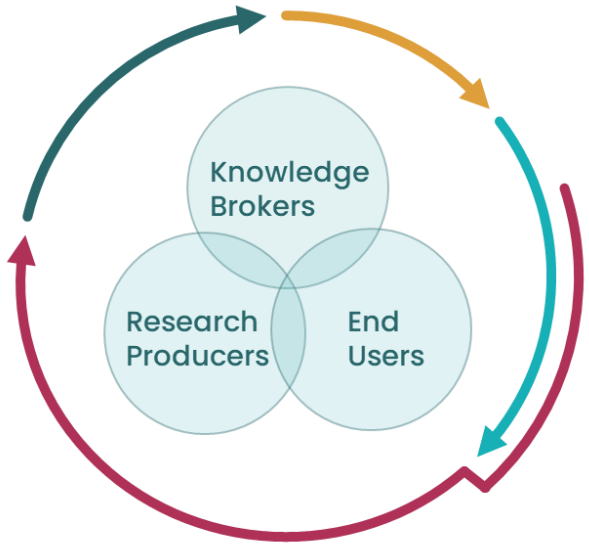
Very promising drug but not much is known about resistance…

- Lab assays showed that HIV with capsid mutations had resistance to LEN (M66I had high-level resistance >1000-fold)[1]
- 2 participants who received low-dose LEN monotherapy developed capsid mutation (Q67H low-level resistance 1.5-fold)[1]
- CAPELLA enrolled individuals on failing ART with multi-drug resistance and gave varying regimens with LEN (n = 72)
  - 8 developed mutations in capsid; 4 resuppressed on LEN[2]
- No infections in PURPOSE 1 LEN for PrEP[3]

1) Margot JAC 2022; 2) Segal-Maurer NEJM 2022; 3) Bekker NEJM 2024

Conclusions

The work we do in MOSAIC will help forge a path forward.



- CATALYST will contribute additional data on magnitude of risks of inadvertent start during acute HIV infection, detection delays and resistance mutations
- Understanding regimen choice and treatment outcomes in individuals who acquire HIV on CAB PrEP will help inform ART guidance after PrEP
- LEN very promising – will be important to monitor for infection and resistance outside of trials

PrEP Saves Lives!

- PrEP is highly successful at preventing HIV infection
- No infection = no resistance!

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MOSAIC HIVDR Study Team and Country Coordinators
John Mellors, Lauren Kudrick, Lisa Levy, country teams in Kenya, Uganda, South Africa, Eswatini, Zambia, Lesotho, Zimbabwe

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All members of the study teams

Individuals and their providers who have generously participated in the GEMS, HPTN, MOSAIC, CATALYST, ACTION and SeroPrEP studies

HIV Drug Resistance Monitoring with PrEP: Implementation & Lessons Learned

EVERLINE BOSEK
MOSAIC HIVDR TEAM

10 SEPTEMBER 2024

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Maximizing Options to Advance Informed Choice for HIV Prevention

Outline

1) Mechanisms to conduct HIVDR monitoring with PrEP
2) Implementation of a national PrEP HIVDR monitoring strategy
3) Challenges and solutions
4) Lessons learned

MECHANISMS TO CONDUCT HIVDR MONITORING WITH PREP

National monitoring vs. implementation studies

- National HIVDR monitoring with PrEP, led by country MOHs: a passive surveillance model to understand the frequency of HIVDR with PrEP use in a country
  - Results can help to inform a public health response to mitigate HIVDR with PrEP use, including informing prevention and treatment programs
- HIVDR monitoring within implementation studies: allows in-depth assessment of seroconversion and drug resistance through stored samples from CAB initiation and follow-up; study sites are limited
  - HIVDR results from implementation studies will add to what was learned from HPTN studies, outside of a trial setting

Mechanisms for HIVDR Monitoring with PrEP

National protocol: In collaboration with MOHs, implement national research protocol to assess HIVDR in PrEP users who become HIV positive. Could be part of standard of care guidance.

Study-specific protocol: Embed HIVDR monitoring of PrEP users within a specific study/project.

Surveillance: Monitoring done periodically, e.g. 3 years according to WHO guidelines

Levy et al Glob Health Sci Pract. 2022; 10(2)

MOSAIC-Supported HIVDR Monitoring with PrEP

National Protocol

Study Protocol

MOSAIC supported national HIVDR monitoring with PrEP


Kenya


Zimbabwe


Eswatini


Lesotho

In Planning


Zambia

Specific to CAB sites

Example: THE CATALYST STUDY

project prep
Integrating PrEP into Comprehensive Services for AGYW

2

IMPLEMENTATION OF A NATIONAL PREP HIVDR MONITORING STRATEGY

Planning for National PrEP HIVDR Monitoring

1. Conduct activities in collaboration with MOH

2. Engage stakeholders (*see next slide*)
   - Protocol team
   - PrEP implementing partners and county/ provincial leadership

3. Create budget and determine logistics, including training strategy
   - Use existing systems, processes, and tools

4. Develop protocol & obtain regulatory and ethical approval

5. Communicate HIVDR plans to PrEP stakeholders
   - Notify county leadership of monitoring plans
     - Ex. NASCOP introduction letters to CASCOs and sub-CASCOs

Examples of Stakeholder Engagement in Kenya

National

- Inform the MOH head of program about the project to create a rapport and support
- Link up with the National PrEP focal person for support
- Participate in regular PrEP/ HIVDR TWGs & provide study updates
- Pro-actively check-in with the MOH on current PrEP engagements
- Offer support to MOH i.e. participate in reviewing guidelines or training

County/Province

- Stay in touch with the county teams to get updates on seroconversion
- Maintain good relationship with county level leadership, utilize existing systems to sensitize counties to the HIVDR protocol
- Plan trainings with county teams
- Train service providers at the facility level
- Conduct site assessments with the county team

Steps to Implement HIVDR Monitoring

- Procure sample collection kits and distribute to sites/ offices
- Create resources, procedural manuals, and job aids to support implementation of HIVDR monitoring
- Conduct training for PrEP service providers
- Initiate sample collection for PrEP users who become HIV positive
- Transport samples to lab for HIVDR testing
- Monitor samples and data collected on a regular basis

Contents of a sample collection kit

Everline Bosek, MOSAIC HIVDR coordinator, conducting training in Mombasa, Dec 2023

Don’t Start from Scratch!
Learn More about Resources to Support HIVDR Monitoring with PrEP

Come to the ‘HIVDR tools and resources’ technical tools orientation on Thursday, September 12th in Room 2!

https://www.prepwatch.org/resources/mosaic-hiv-drug-resistance-monitoring-program/

3 CHALLENGES AND SOLUTIONS

Challenges Encountered in Conducting National HIVDR Monitoring of PrEP Users

- Training of all PrEP sites
  - As PrEP sites expand, it can be difficult to ensure there is a service provider trained at every PrEP site
- Missed seroconversion cases
  - Initiating or continuing PrEP when an individual is in an acute HIV infection phase
  - Not all service providers may be aware of HIVDR monitoring procedures
  - Some PrEP users who acquire HIV may decline sample collection or be lost to follow up
- Data accuracy
  - PrEP seroconversion numbers may differ from the number of seroconversions captured within external public health monitoring systems
- Sample transport
  - Stringent time requirements for sample processing
  - Limited dry ice availability

Challenges and solutions

- Training of all PrEP sites
  - Embed training on PrEP HIVDR monitoring procedures into ongoing national MOH PrEP trainings
  - Utilize existing systems to cascade trainings (using train the trainer approaches) and prioritize PrEP sites in high HIV incidence areas
  - Conduct refresher training as needed either virtually or in-person
- Missed PrEP seroconversion cases
  - Ensure training plan is as comprehensive as possible
  - Support PrEP sites to screen clients for acute HIV infection
- Data accuracy
  - Work with implementing partners and MOH to conduct regular comparisons of PrEP seroconversion data

Challenges in sample transport

- HIVDR monitoring with CAB PrEP requires whole blood to arrive at the laboratory for plasma processing within 24-48 hours
  - Consider intermediary processing lab for plasma preparation, storage at -80°C and then further transport to testing lab (on dry ice)
  - Work with in-country couriers to plot out PrEP site locations and ability to reach processing or testing lab
  - Conduct dry runs for distant sites
  - Remain vigilant and monitor transport delays and sample integrity
- For plasma shipment: Dry ice is expensive and may not be readily available
  - Consider use of reuseable Techni Ice packs

4 LESSONS LEARNED

Lessons Learned from Implementation of National PrEP HIVDR Monitoring Studies

- ✓ Collaboration with MOH for buy-in and support of HIVDR monitoring is key for successful uptake from PrEP sites
- ✓ Engage PrEP stakeholders (IPs, county/ provincial leadership) throughout the project implementation process to ensure timely reporting of seroconversion cases
- ✓ Participate in national/ regional PrEP and HIVDR TWGs to update stakeholders and troubleshoot implementation issues in real-time
- ✓ Support MOH and writing teams of national guidelines by participating and contributing towards the development or review of PrEP/ HIVDR strategic framework and guidelines

ACKNOWLEDGMENTS

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Photo Credit: MOSAIC Consortium

Experiences with HIVDR Monitoring in Kenya

Dr. Jonah Onentiah
HIV Prevention Manager
National AIDS/STI Control Program (NASCOP)
Ministry of Health, Kenya

10 September 2024
AFRICA REGIONAL PrEP WORKSHOP

Outline

- Background: PrEP Uptake in Kenya
- Overview and role of HIVDR monitoring for PrEP in Kenya
- Future of HIVDR monitoring with new PrEP products

Background : Overview of PrEP Implementation In Kenya

- PrEP officially launched in 2017 , Framework on the implementation & PrEP Toolkit developed & launched later revised in 2022
- All this fit in the national strategic plan as follows;
  - **Kenya HIV Prevention Revolution Roadmap, 2014** – Outlines the roadmap in reduction of new HIV infections by 2030
  - **Kenya AIDS Strategic Framework II,** – KASF II has four strategic directions for tackling the HIV pandemic in the country. The Strategic direction 1: focuses on reducing new HIV infections
  - **Kenya HIV Prevention & Treatment Guidelines** (2022) – Provides guidelines on implementation of PrEP for HIV prevention
  - **Pre-exposure Prophylaxis for the Prevention of HIV infection: A Toolkit for Service Provider (2022)** – Outlines the process, systems and measures in provision of PrEP

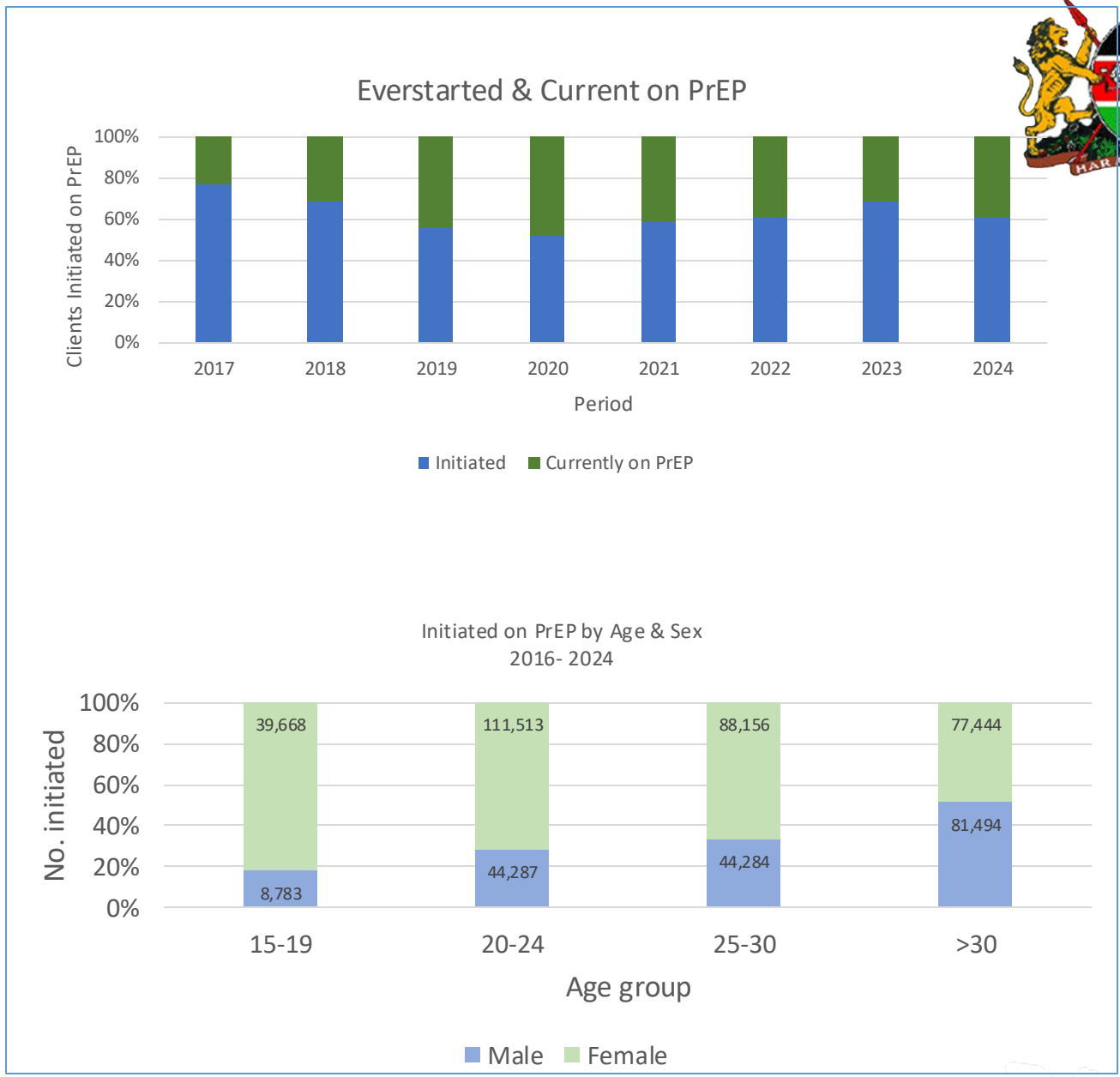
Objectives & Achievement

Objective	• Key Achievements
Availability	• PrEP is offered in over 2000 facilities • Studies ongoing for Online & Private Pharmacy delivery
Acceptability	• Over 600,000 reported to have ever initiated on PrEP • Rising and varying level of awareness among different populations • Services available at no cost to clients
Accessibility	• Enabling policy environment for service delivery • Trained providers
Holistic integration to combination prevention	• PrEP offered as one of the choices in the HIV Combination prevention package

NASCOP

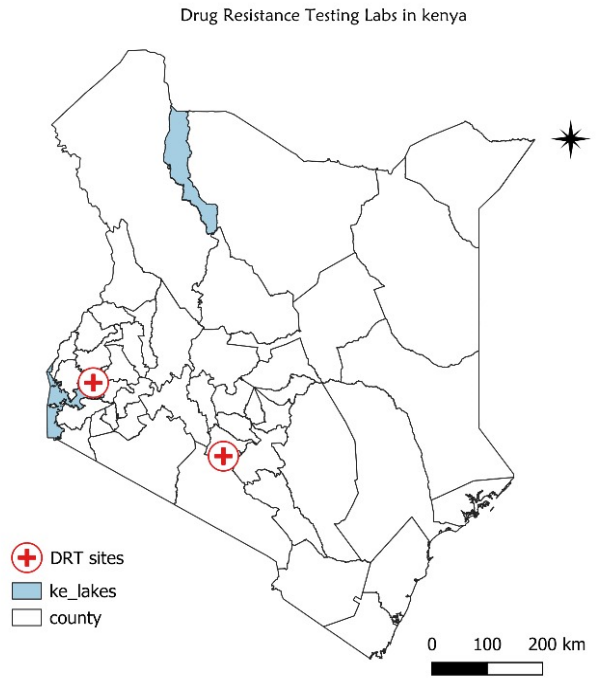
Background : PrEP Implementation In Kenya

- Service Delivery coordinated by the National HTS/PrEP TWG convened quarterly
- Focus areas for implementation
  - Leadership & governance
  - Service Delivery
  - Communication, advocacy & community engagement
  - Health Products & Technologies
  - Strategic Information
  - Resource mobilization & financing
- PrEP currently available across the country with over 2000 facilities offering services
- Uptake notably higher among females & general population



HIV Drug Resistance Monitoring in Kenya

- HIV DR monitoring has been made a standard of practice for all PrEP users who test HIV positive
- Testing offered in central labs with strengthened sample transport network across the country
- Coordination done through collaboration between health care workers, County AIDS & STI Coordinators & implementing partners
- Guidelines describe the protocols care for all PrEP seroconverters
- Data collected and reported on the National Platform KHIS on a monthly basis
- For EMR sites the data is pushed to National data house
- Data disaggregated by age sex and population typology



DRT labs : NHRL (Nairobi) KEMRI Kisumu

Findings from national PrEP HIVDR Monitoring in Kenya from 2018-2021 (GEMS)

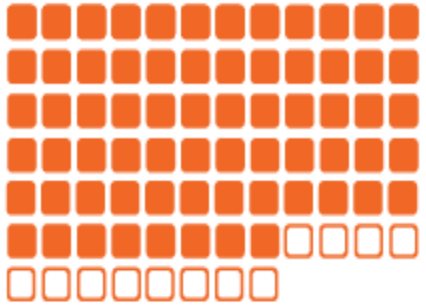
In July 2017, oral pre-exposure prophylaxis (PrEP) was rolled out nationally in Kenya as part of combination HIV prevention. From 2018-2021, the National AIDS and STI Control Programme (NASCOP), Ministry of Health in collaboration with the Global Evaluation of Microbicide Sensitivity (GEMS) project, conducted a national cross-sectional HIV drug resistance monitoring study.

The Kenya PrEP Seroconversion Protocol assessed the frequency of HIV drug resistance mutations among individuals who became HIV positive after starting oral PrEP.

SAMPLES COLLECTED

68 Samples collected from

80 Individuals who became HIV positive while on PrEP



In cooperation with:

- County AIDS and STI Coordinators (CASCO)
- Jilinde, LVCT Health, SWOP, Centre for Health Solutions, CHAK and other organizations providing PrEP

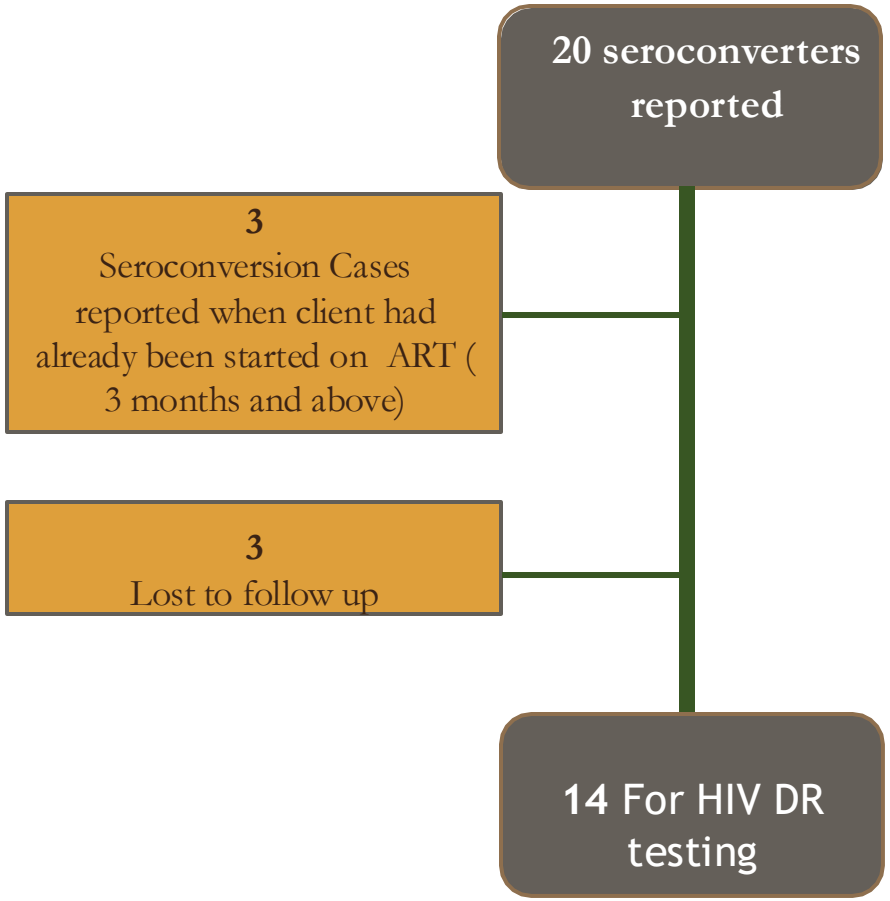
KEY FINDINGS

- Rate of seroconversion is low (**80 cases among ~ 58,200 PrEP users**)
- **34 samples successfully genotyped** for HIVDR
- Resistance to tenofovir was not detected (K65R mutation)
- Emtricitabine-associated **M184V mutation detected in 18% of samples** (6 of 34), highlighting the importance of monitoring for HIVDR in PrEP seroconverters
- **Incidence of NNRTI resistance (29%; 10 of 34)** warrants monitoring, particularly with planned rollout of dapivirine vaginal ring

NASCOP

MOSAIC – HIV DR - Preliminary Data

- A total of 20 PrEP seroconverters reported (Jun 2021 – June 2024)



Participants Characteristics: N= 14

- Gender: majority are female (10/14)
- #days between initiation and Seroconversion;
  - Majority >60 days.
  - Only one had used PrEP for <40days
- Key population Classification:
  - Majority are in sero-different relationship
- PrEP Method Used:
  - 13 Oral PrEP users
  - 1 Dapivirine PrEP ring user
- Sample Type
  - Dried blood spots (DBS) or plasma

NB: Project is still ongoing.

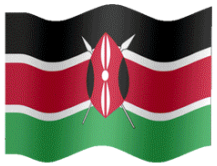
How has Kenya utilized PrEP HIVDR data?

- Assessed overall PrEP program effectiveness
- Strengthening to increase in-country lab capacity at the national laboratory to perform HIVDR testing from diverse samples, i.e. Dried Blood Spots
- Inform policy decision : From 2018, DRT was accessed through GEMS Study, the findings demonstrated need for policy & DRT was included in the Kenya HIV Prevention & Treatment Guidelines 2022.
- Structured data visualization on the national data warehouse
- Shared initial PrEP HIVDR monitoring data with WHO and Global Fund

Future of HIVDR Monitoring in Kenya

- Building off success of HIVDR monitoring for oral PrEP, Kenya plans to provide HIVDR monitoring for other PrEP products i.e. LA CAB PrEP and Dapivirine Vaginal ring
- Integration of DRT for PrEP with other DRT (conducted for clients with treatment failure)
  - Currently DRT for PrEP is mainly conducted through MOSAIC
- Continued collaboration among stakeholders
- Documentation of evidence

How HIV DR Data will be Utilized



Thank you!

NASCOP