HIV Updates in 2023: History, Epidemiology, Treatment, Prevention, Cure, Vaccine

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MIDWEST AIDS TRAINING + EDUCATION CENTER

AETC AIDS Education & Training Center Program Midwest

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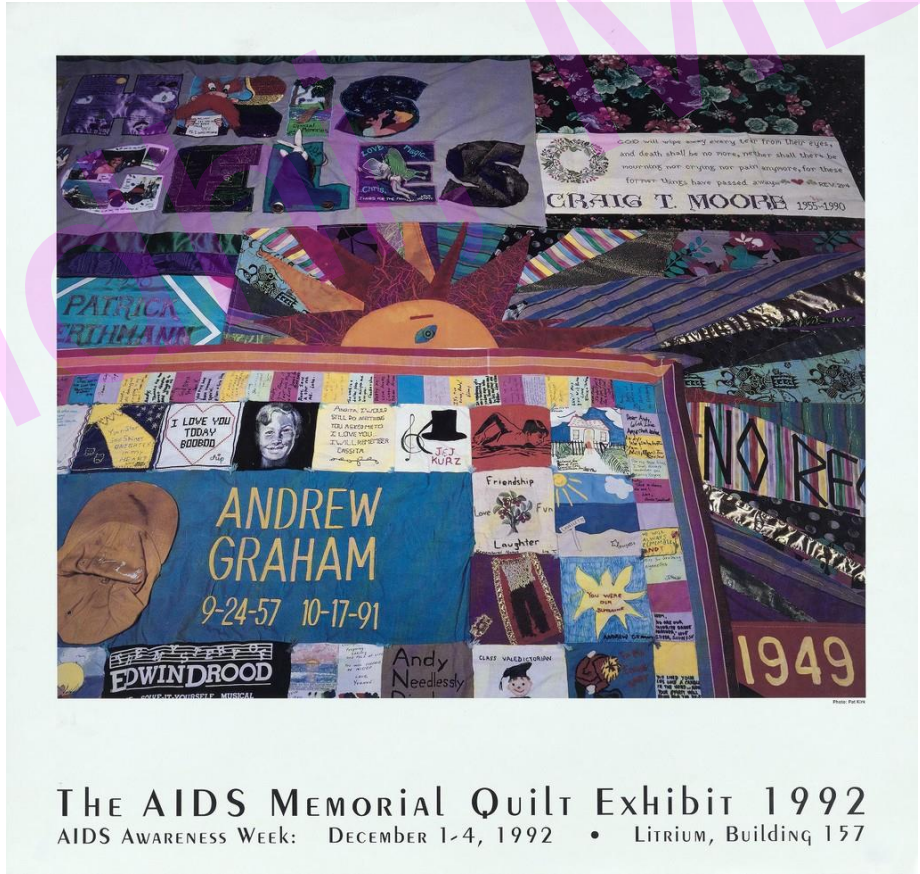
Speaker Disclosures

No financial disclosures.

Learning Objectives

- Review the history of HIV and how looking back helps us look forward.
- Discuss updates in HIV treatment in 2023.
- Discuss advances in HIV prevention in 2023.
- Recognize where we are in HIV cure and HIV vaccine advances.



HISTORY, EPIDEMIOLOGY, CARE TRENDS

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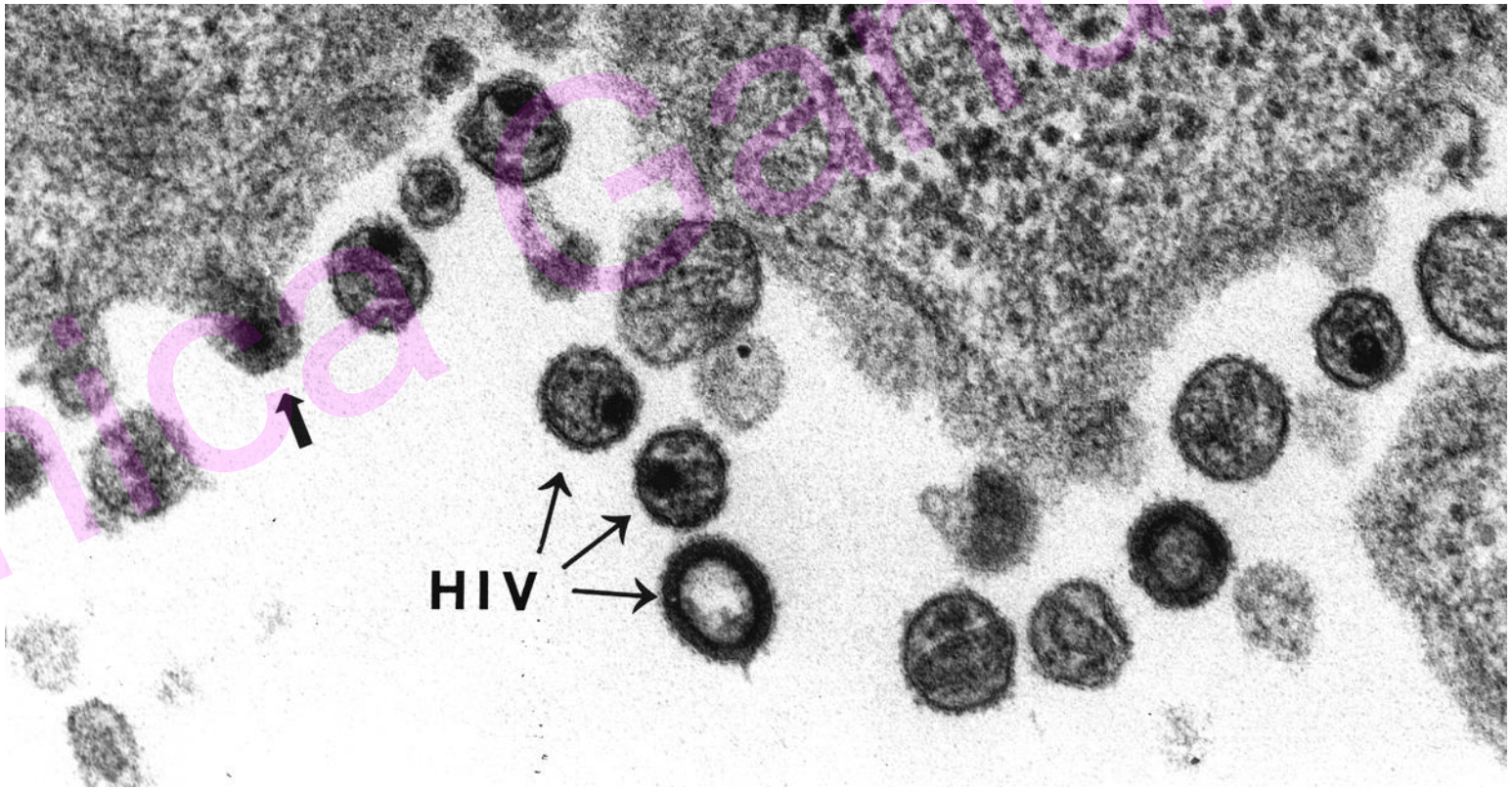
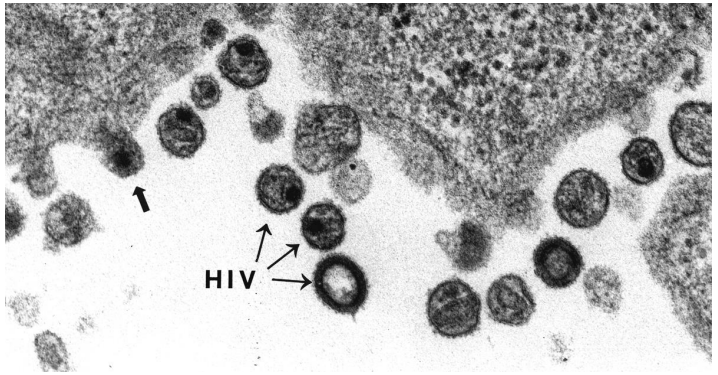
What type of virus is HIV?

- HIV – “lentivirus”, subgroup of retroviruses
  - **Lenti**virus means SLOW virus (long interval between initial infection and onset of serious symptoms)



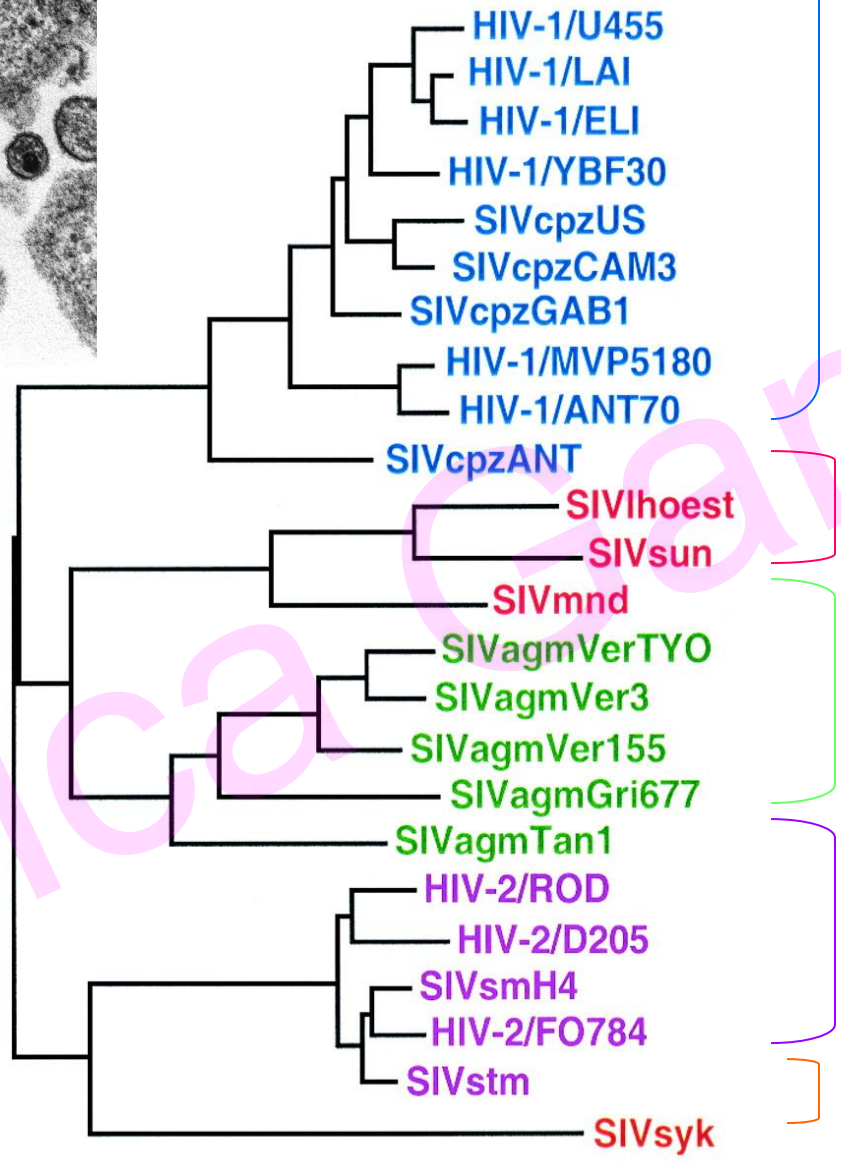
To trace origins, where do we see retroviruses (lentiviruses) in our closest relatives?



From where?

How?

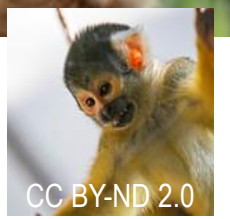
When?



1) Chimpanzees, Gorillas

2) Monkeys; Mandrills

3) African Green Monkeys, Baboons

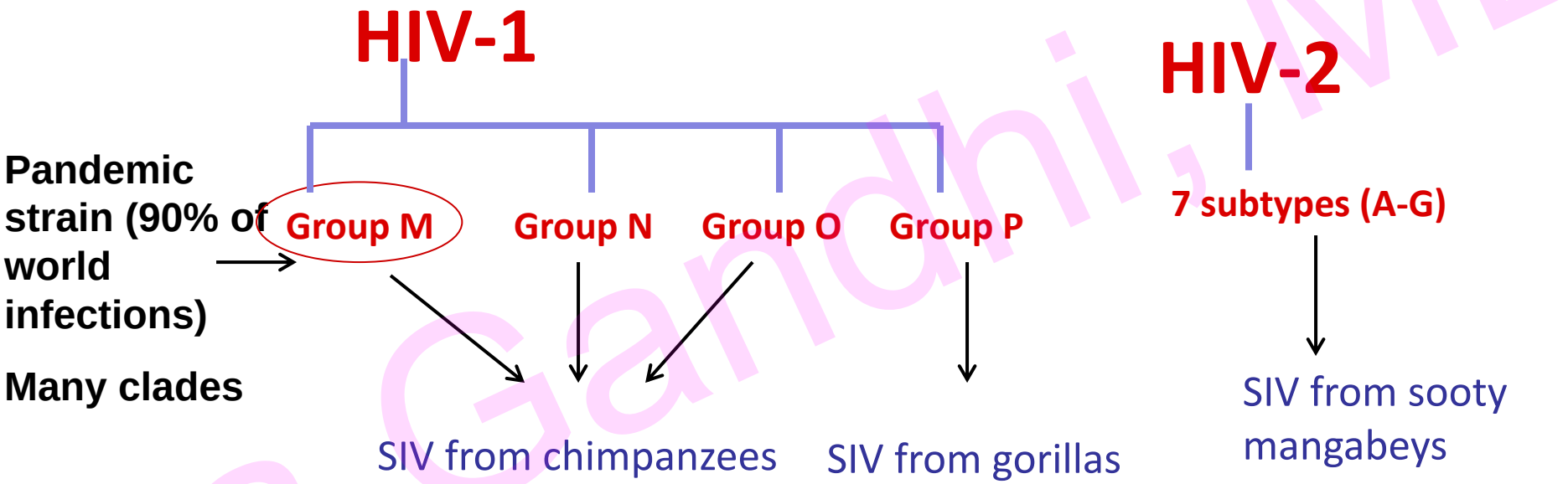


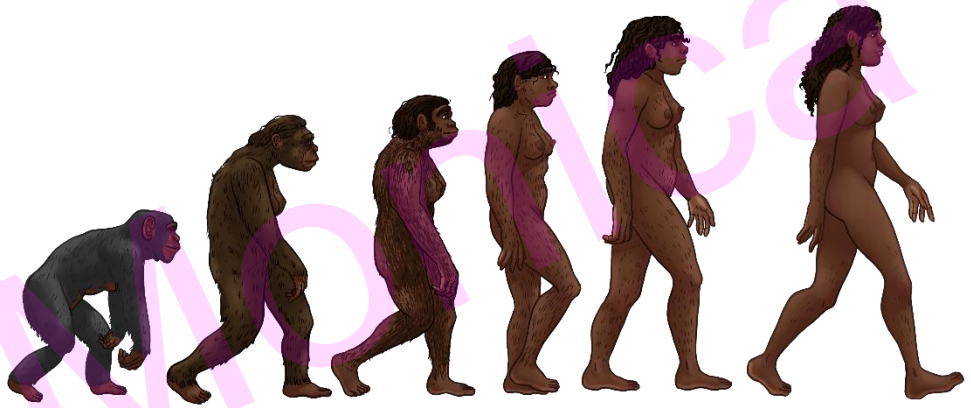
4) Sooty Mangabeys

5) Sykes' Monkeys

Hahn BH. AIDS as a Zoonosis: Scientific and Public Health Implications. Science 2000

How did HIV-1 and 2 get from primate host to us?





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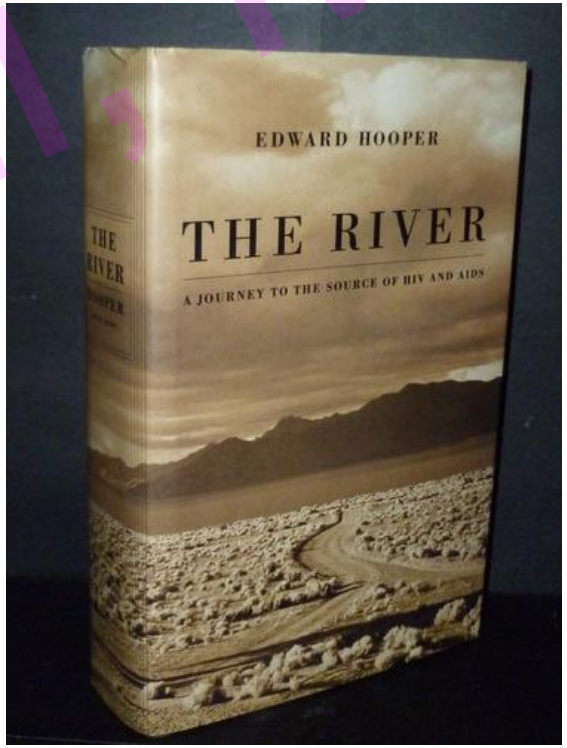
UIC-Adobe-Picsart

First theory – "The River"

- *The River: A Journey to the Source of HIV and AIDS* (Edward Hooper, 1999)
- Polish scientist competing with Sabin for first oral polio vaccine (Sabin won)
- Scientist (Koprowski) administered his vaccine to 1 million people in Belgium-controlled Africa
- Likely not reason (wrong primate; wrong timing) but led to greater safety with primate cells



Plotkin SA. CHAT oral polio vaccine was not the source of human immunodeficiency virus type 1 group M for humans. *Clin. Infect. Dis 2001*

What was the cross over event?

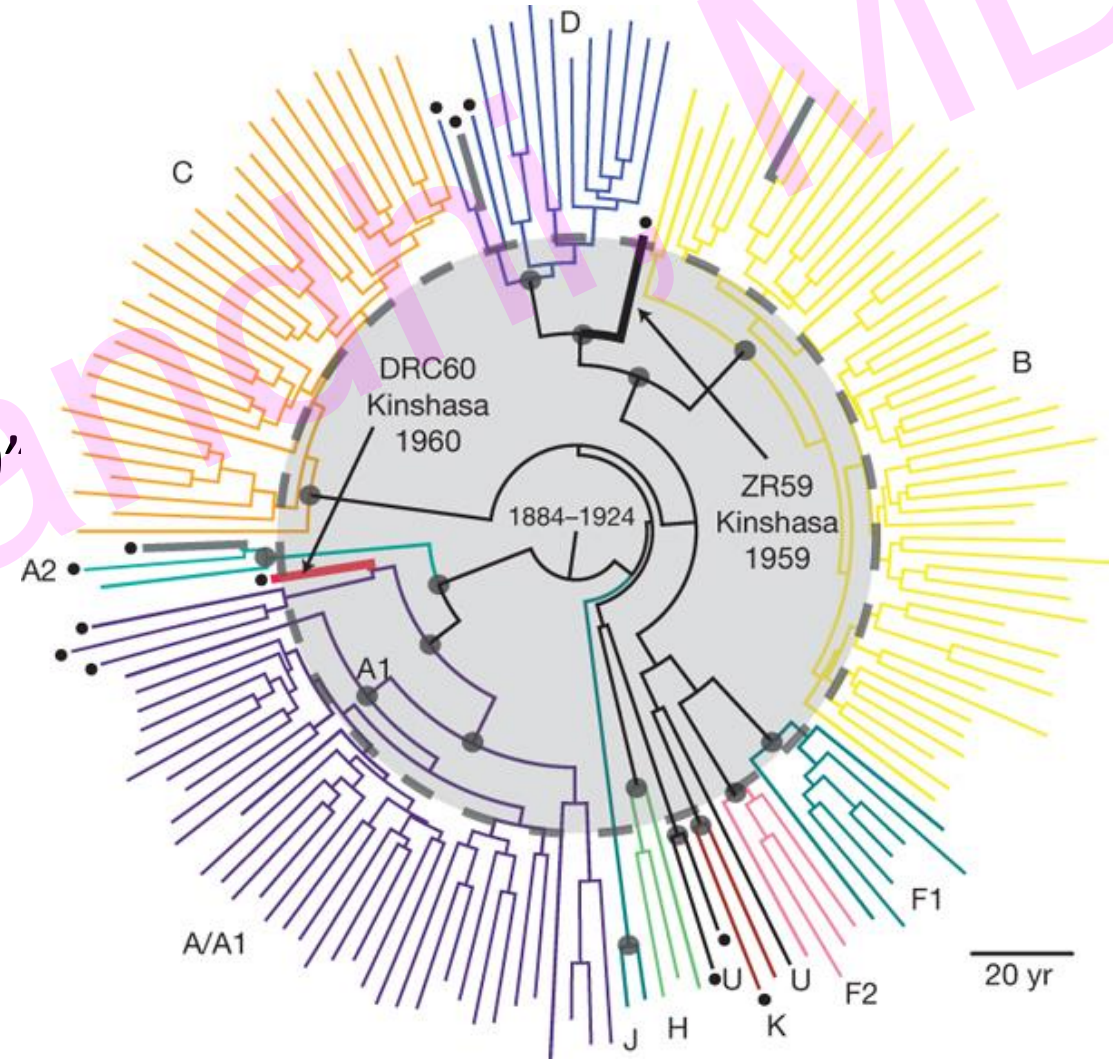
- Likely “bushmeat” trade- hunting primates for food
- Hunters and other highly exposed populations: many SIV strains incorporated
- General human population – one cross over event and SPREAD due to social disruption, colonization with establishment of sex trade, city growth

% HIV-positive persons in 17 rural villages, Cameroon

Hahn BH. AIDS as a Zoonosis. Science 2000; Le Breton M. Wolfe N. Exposure to wild primates among HIV-infected persons. Emerg ID 2007

When did it get to us? Two human specimens

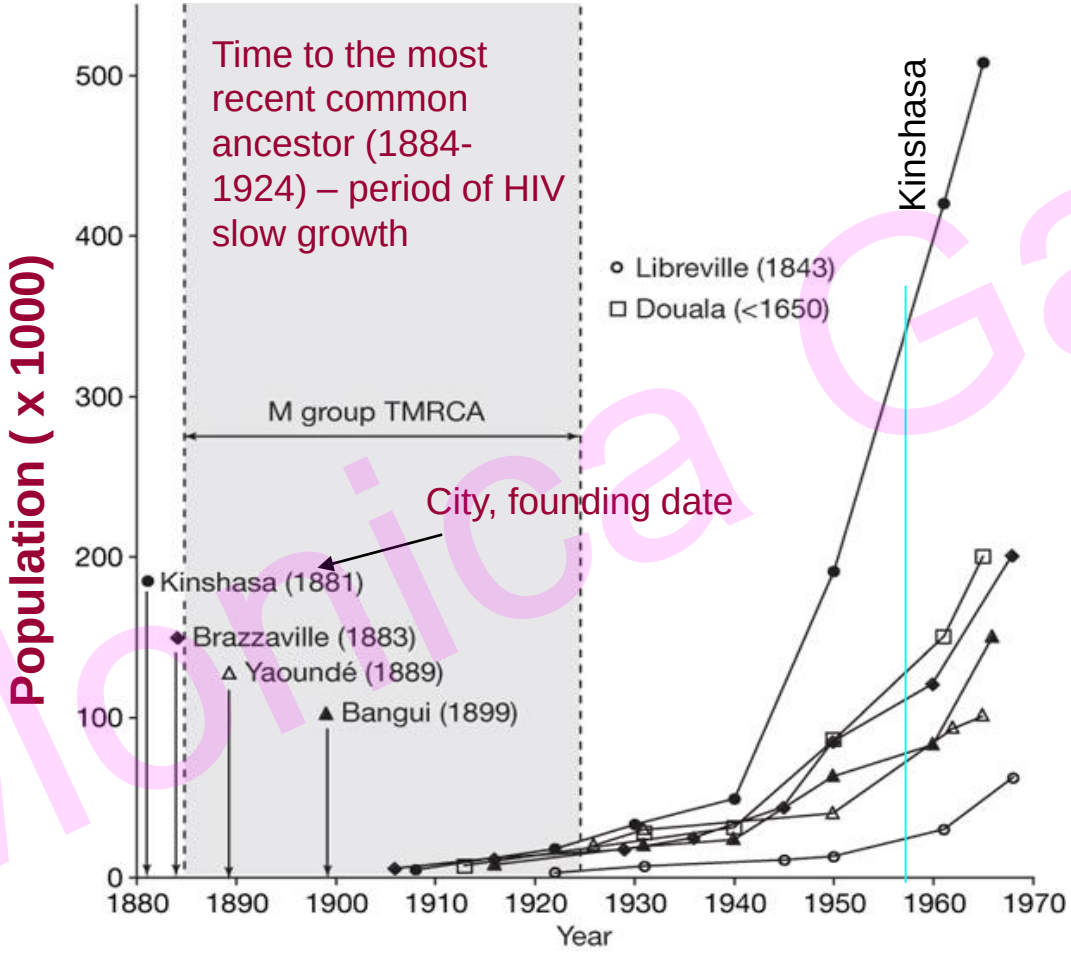
- Blood specimen with HIV from 1213 specimens in “Zaire” collected & stored at UW from 1959 (ZR59)
- Lymph node in paraffin with HIV, adult female, Kinshasa, 1960 “DRC60”
- DRC60 very different than ZR59
- Family tree constructed; rate of mutation calculated
- Ancestor of HIV-1 M probably entered humans 1884-1924



Hahn B. Science 2000; Worobey M. Direct evidence of extensive diversity of HIV-1 in Kinshasa by 1960. Nature 2008

nature

The rest is West African history

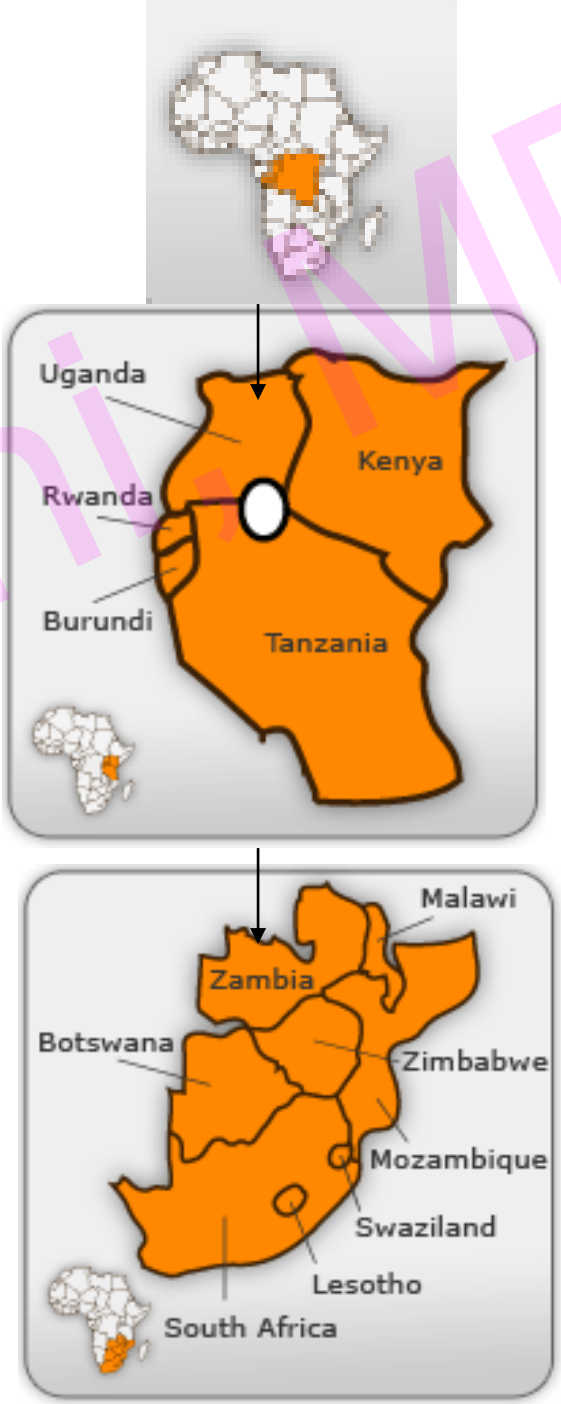


- No city in region before 1910 had population > 10,000
- Kinshasa (and other) populations ↑ in 2nd half of 20th C. (trade, colonial)
- HIV-1 M from Cameroon brought by traveler down-river to Kinshasa – entered urban sexual network and spread
- By 1960's, ~2000 people infected in Africa
- By 1970s, first probable outbreak in Kinshasa (OIs seen)

Worobey M. Nature. 10/08

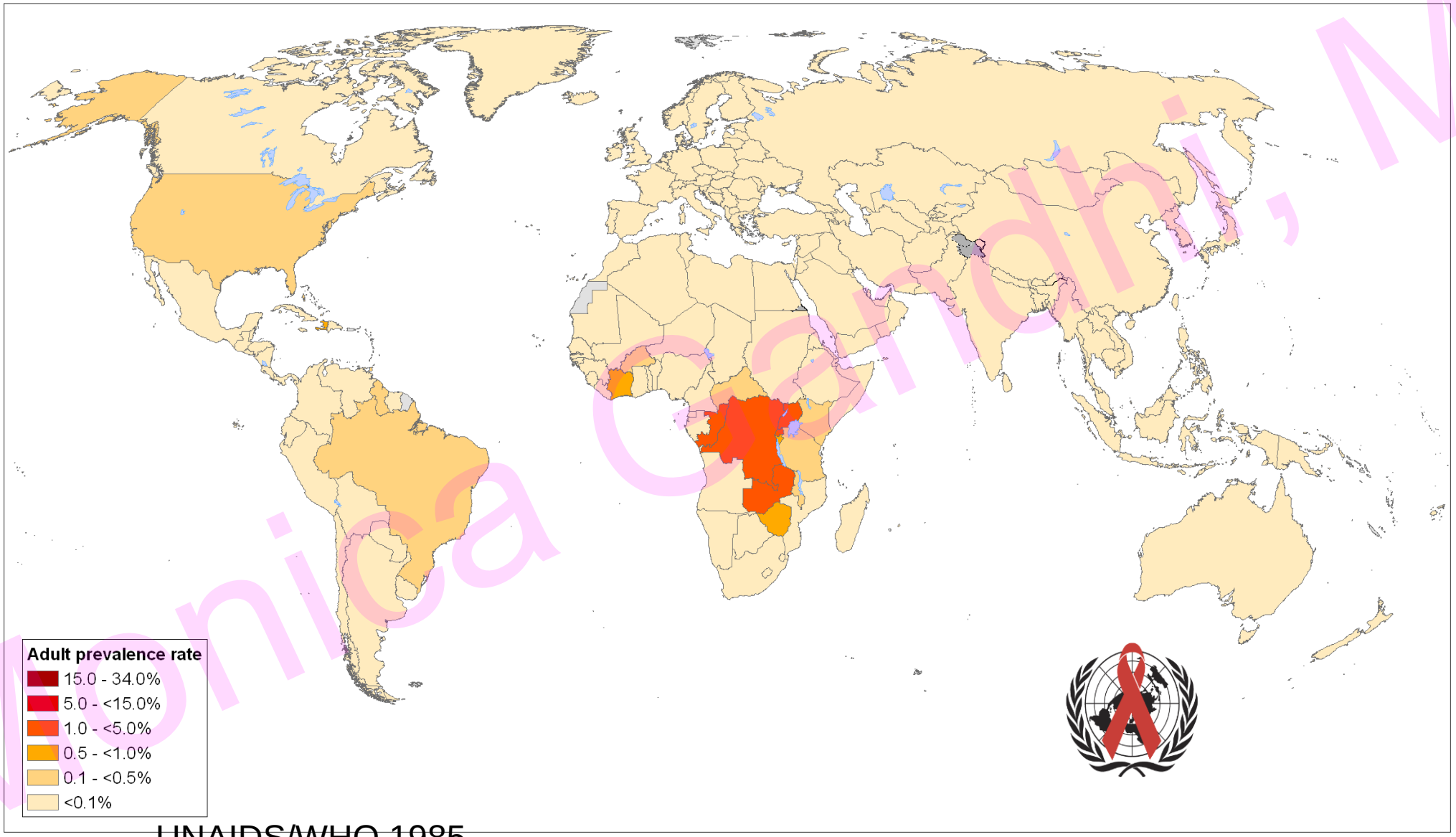
What happened from there?

- Carried from West to Eastern Africa in ’70’s
- Spread fast in E. Africa, epidemic form in early ’80’s
  - Labor migration (35% truck drivers positive Uganda ’88)
  - High ratio of men, urban centers, sex trade, STDs
  - Low status of women, low rates circumcision
  - 85% Nairobi sex workers infected by 1986)
- By mid and late ’80’s, on to sub-Saharan Africa
  - Tanzam road between Tanzania and Zambia



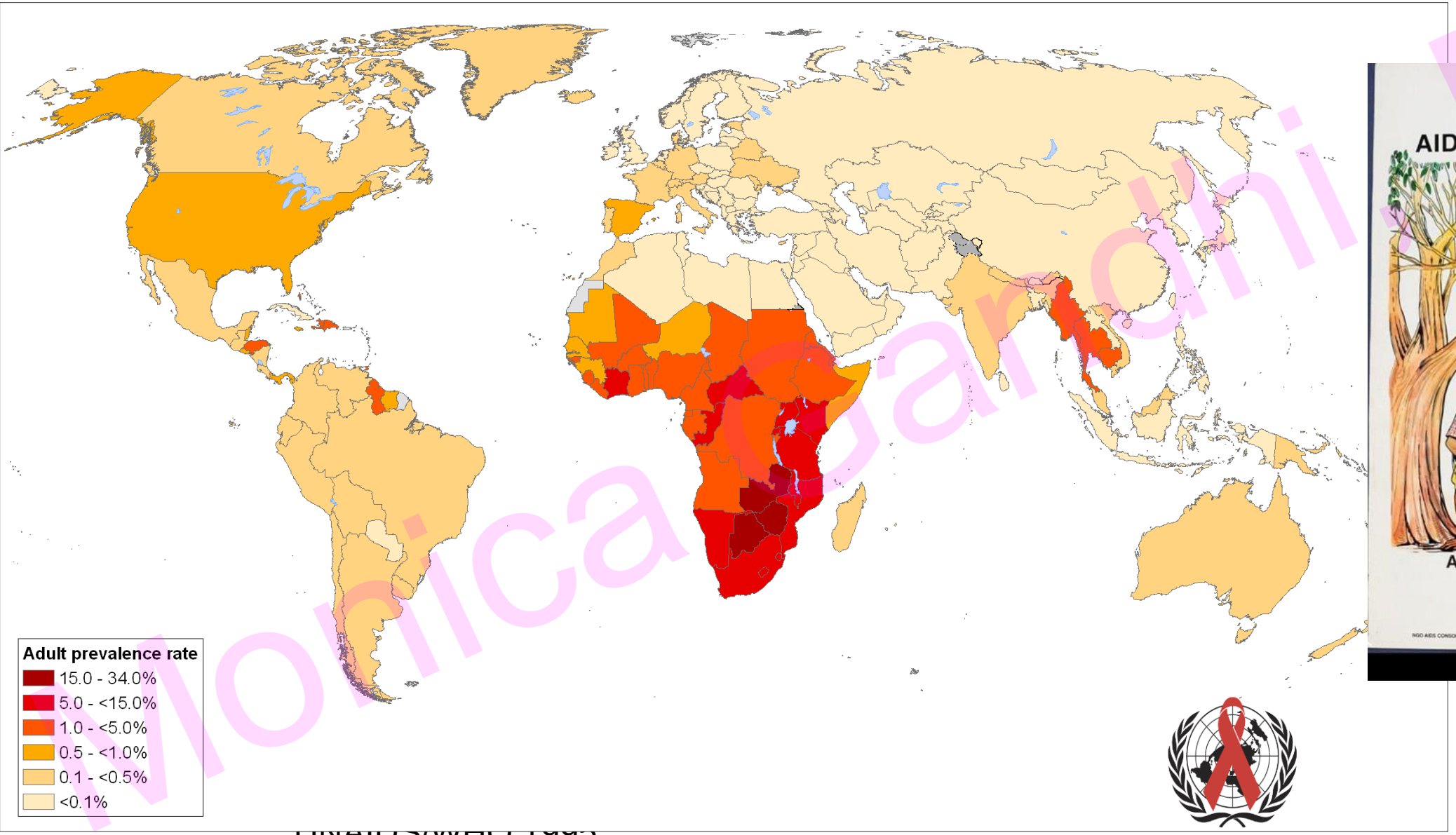
Piot P. Retrospective seroepidemiology of AIDS virus infection in Nairobi populations. Journal of Infectious Diseases 1987

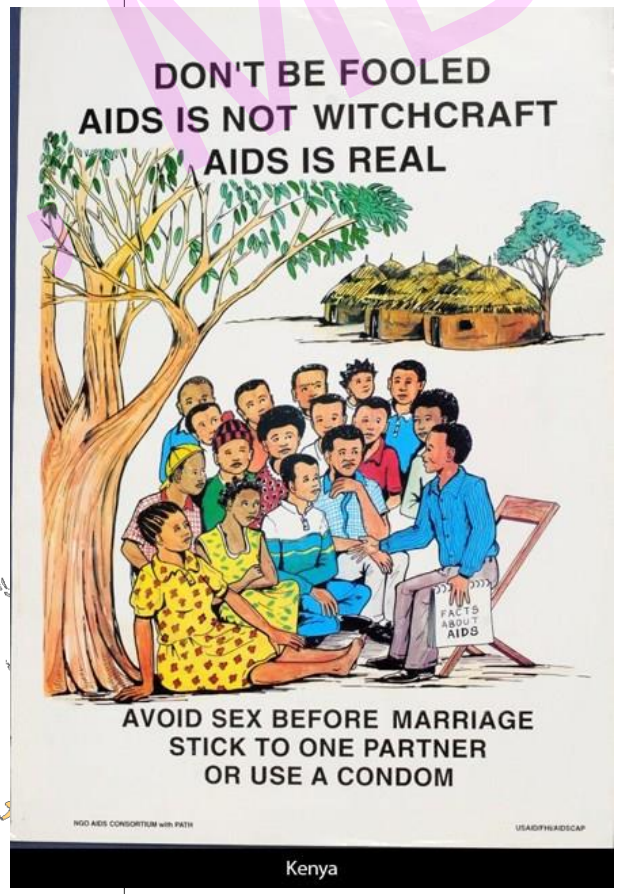
Global HIV prevalence in adults, 1985



UNAIDS/WHO 1985

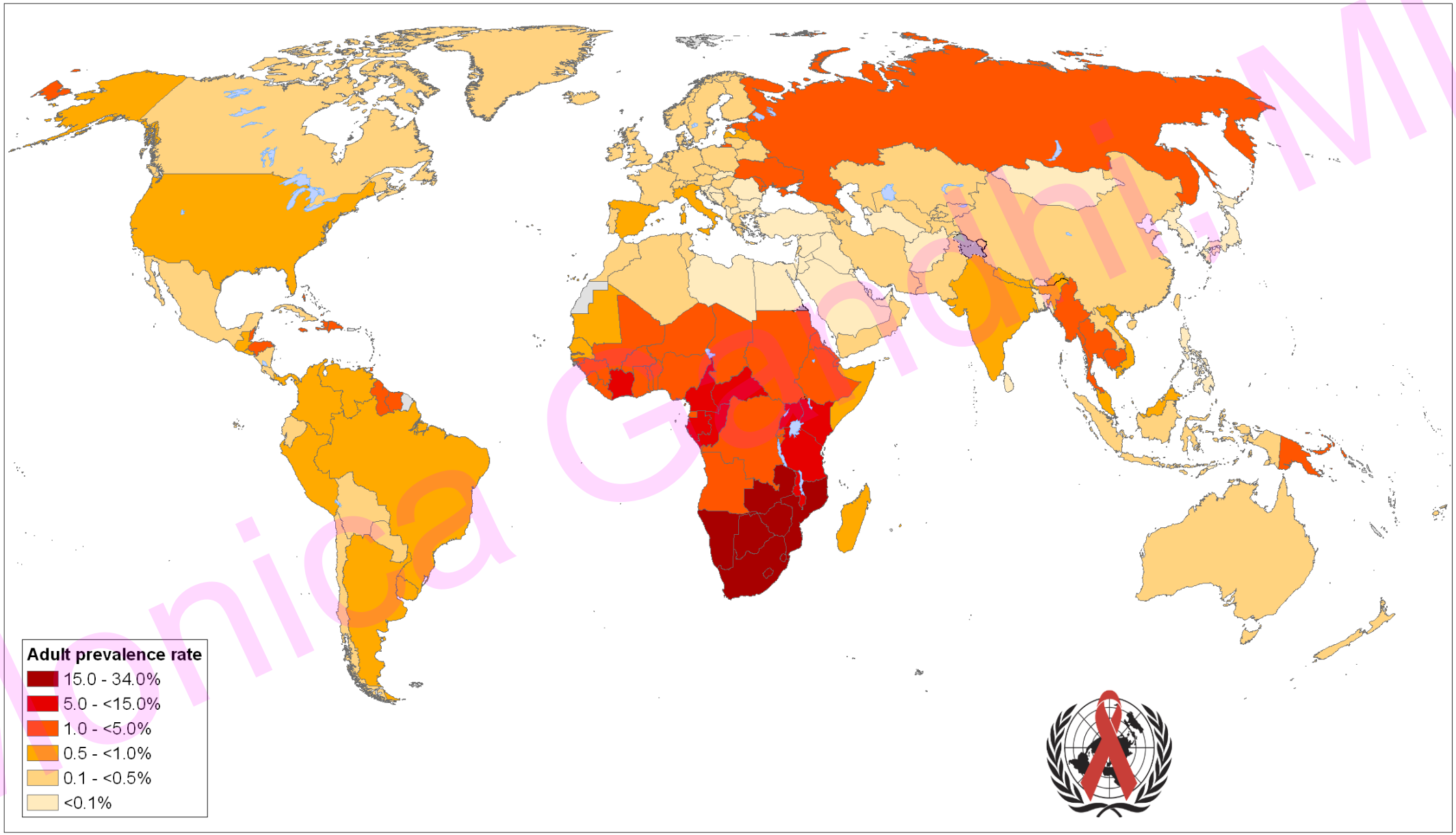
Global HIV prevalence in adults, 1995





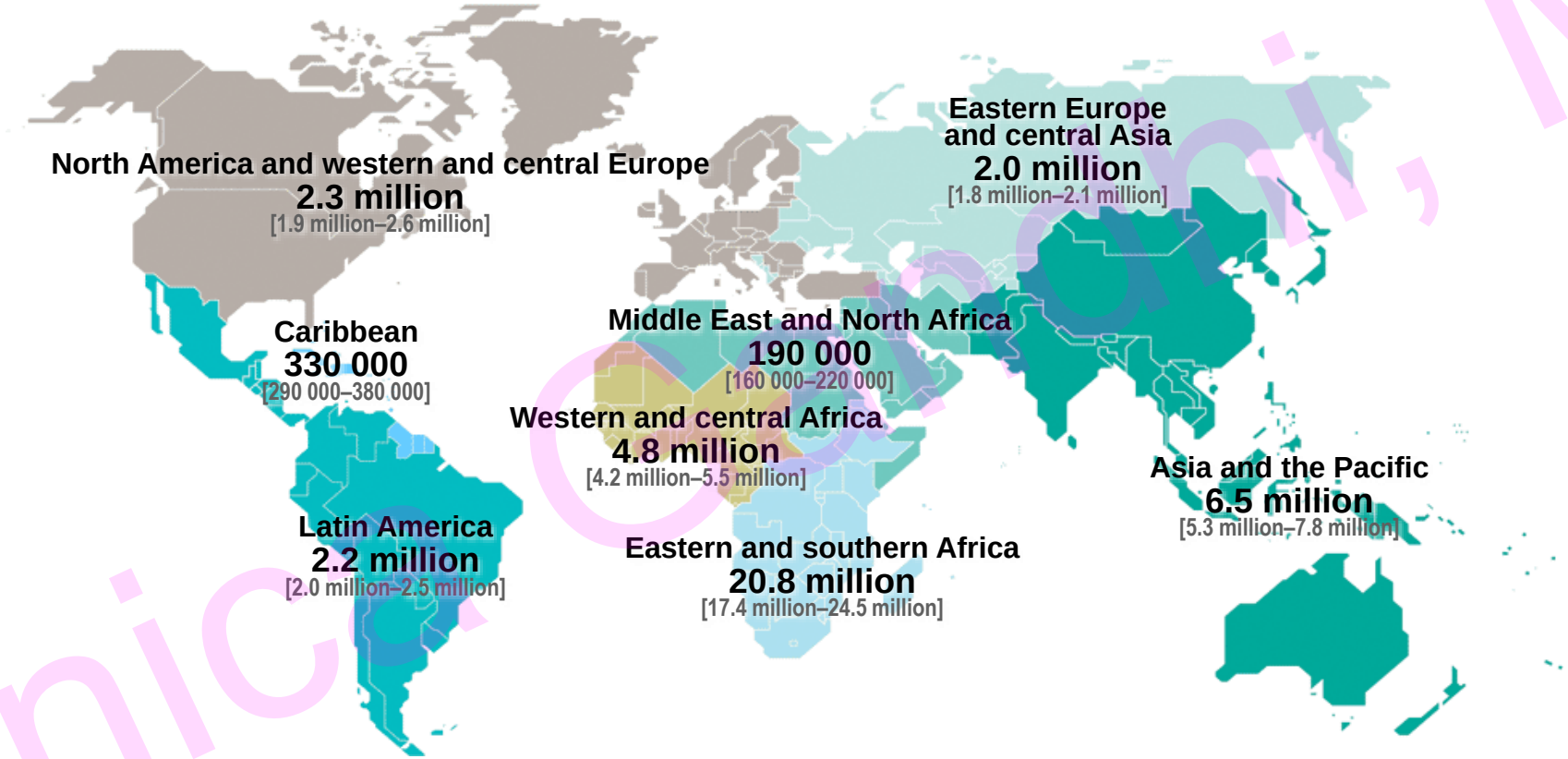
UNAIDS/WHO 1995

Global HIV prevalence in adults, 2005



UNAIDS/WHO 2005

Adults and children estimated to have HIV 2022



Total: 39.0 million [33.1 million–45.7 million]

UNAIDS

UNAIDS Global AIDS Update 2022

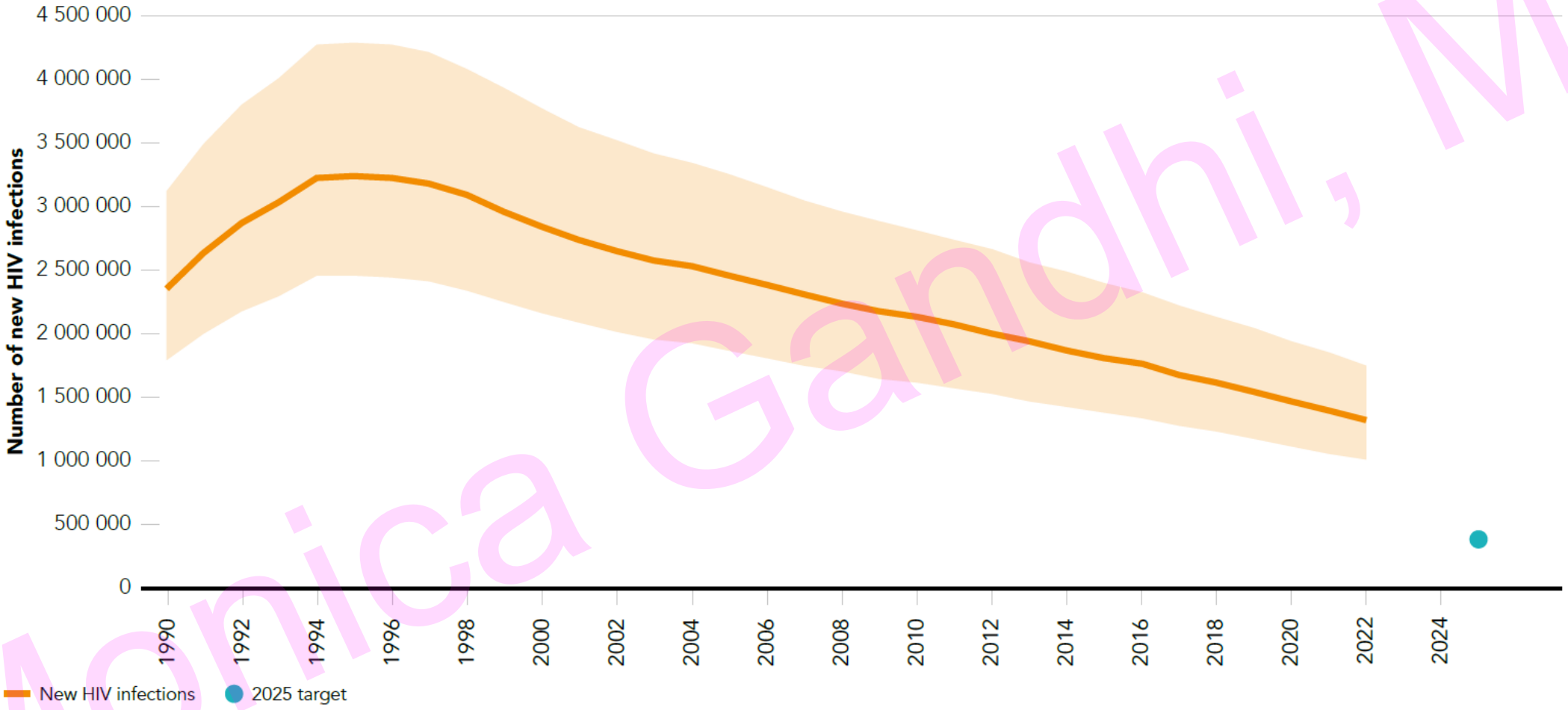
UNAIDS: Major setbacks to HIV response during COVID (TB, malaria, etc.)

38.4 million people with HIV (highest), 1.5 million new infections last year, 650K deaths last year, 40.3 million deaths total, only 75% of adults (52%) children have ART access; with millions of girls out of school, had increase (young woman infected every 2 minutes)

Global estimates for adults and children 2022

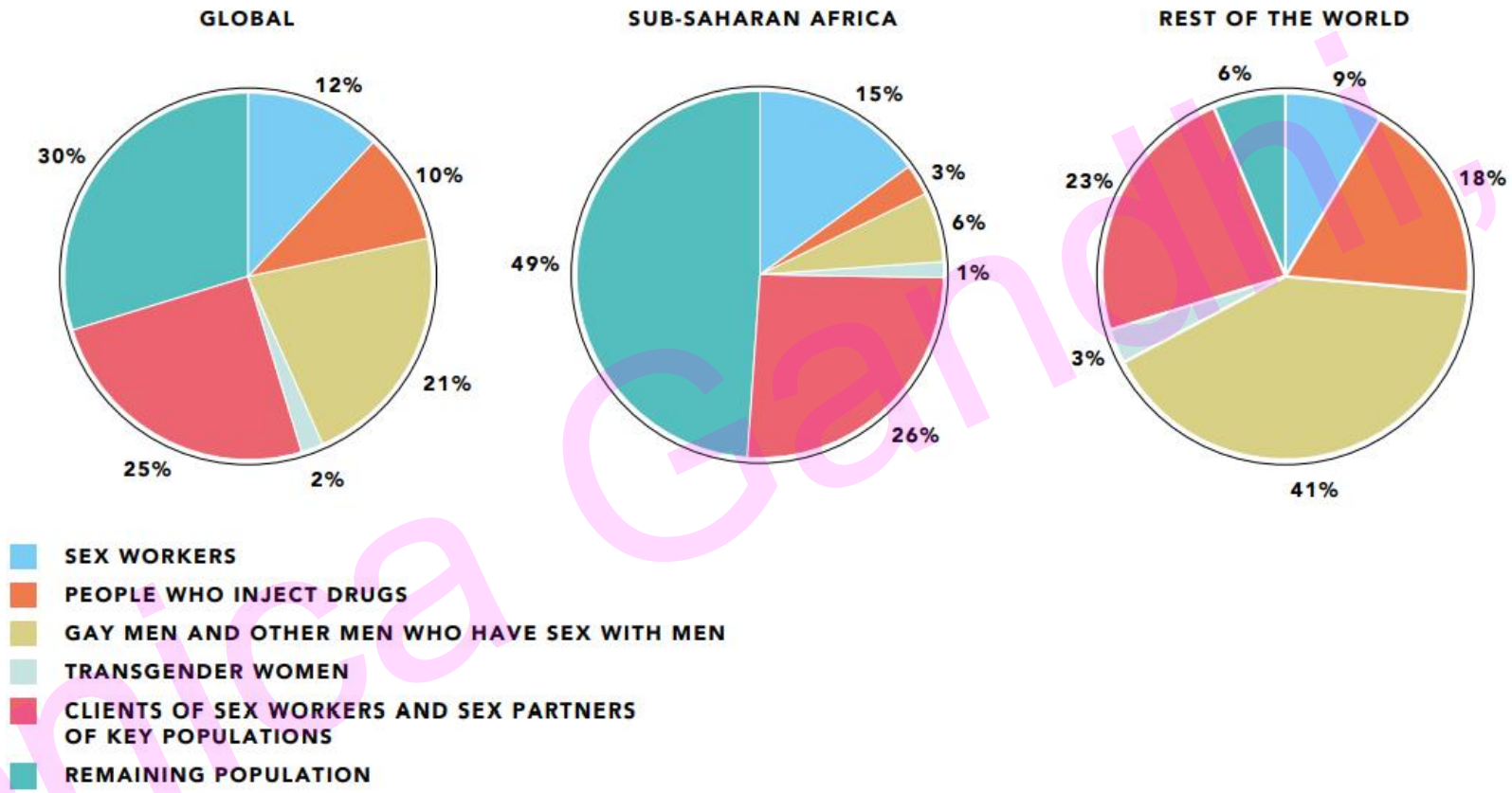
People with HIV	**39.0 million**	[33.1 million–45.7 million]
New HIV infections	**1.3 million**	[1.0 million–1.7 million]
Deaths due to AIDS	**630 000**	[480 000–880 000]

Figure 12.1 Number of new HIV infections, global, 1990–2022, and 2025 target



Source: UNAIDS epidemiological estimates, 2023 (https://aidsinfo.unaids.org/).

Distribution of acquisition of new HIV infections by population, global, sub-Saharan Africa and rest of the world, 2021



Source: UNAIDS special analysis, 2022 (see Annex on Methods).

Note: Due to variations in the availability of data from one year to the next, we do not provide trends in this distribution. See Annex on Methods for a description of the calculation.

UNAIDS

HIV in the United States

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First clinical descriptions of AIDS, MMWR

1981 June 5;30:250–2

MMWR

Pneumocystis Pneumonia — Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

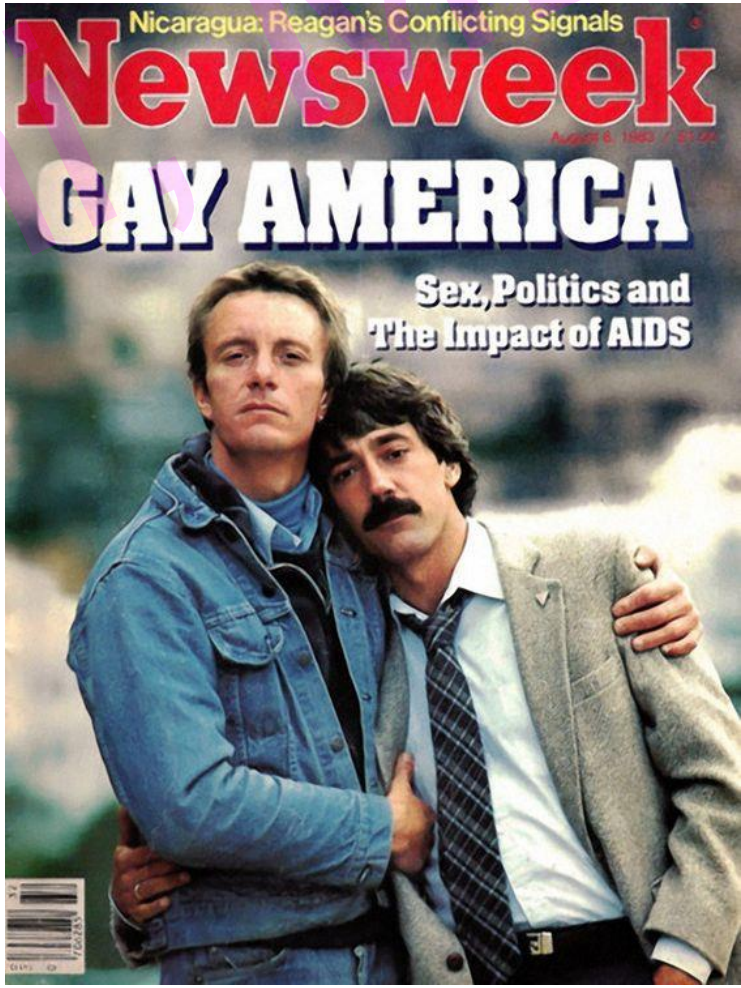
1981 July 4;30:305–8

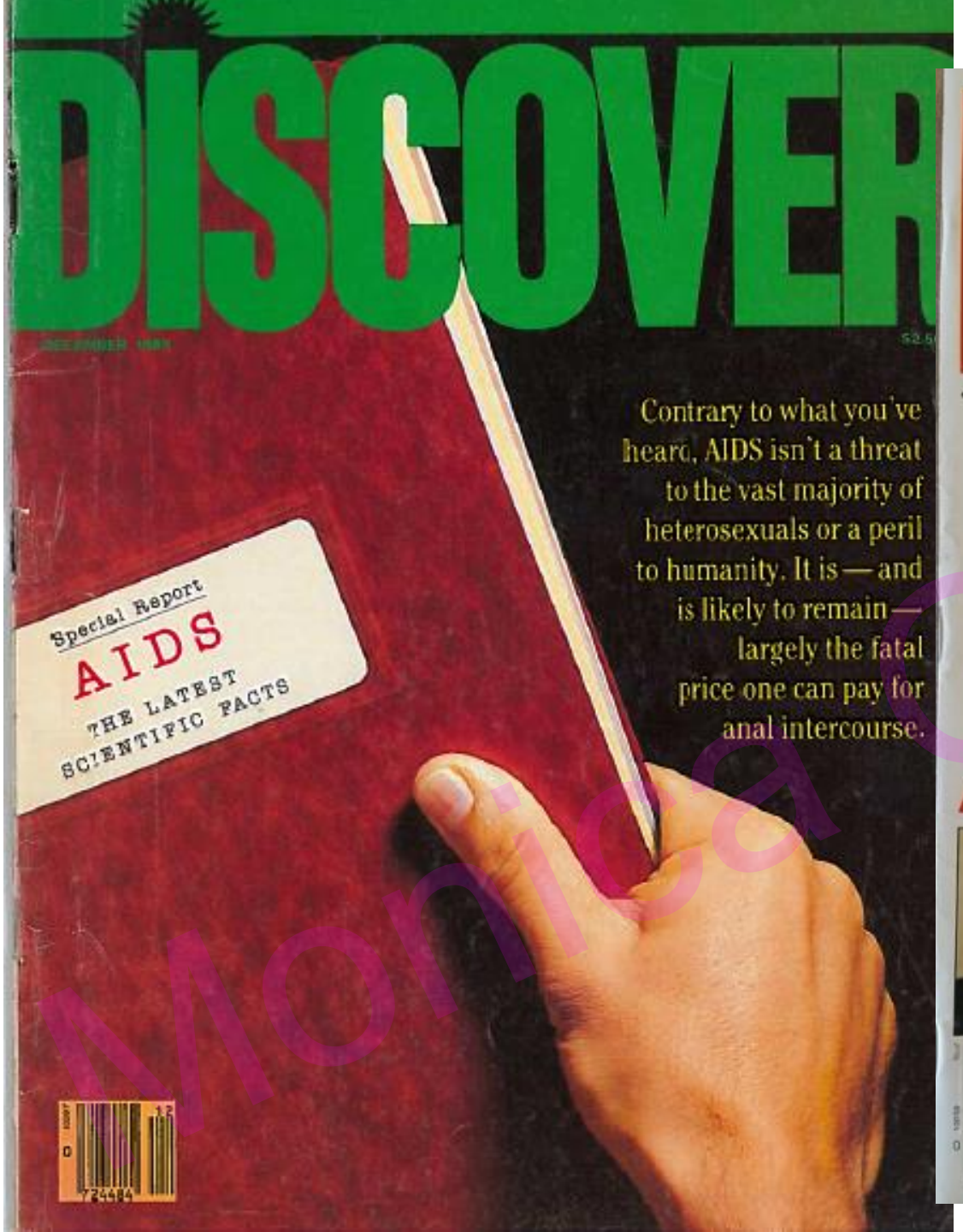
Kaposi's Sarcoma and *Pneumocystis* Pneumonia Among Homosexual Men — New York City and California

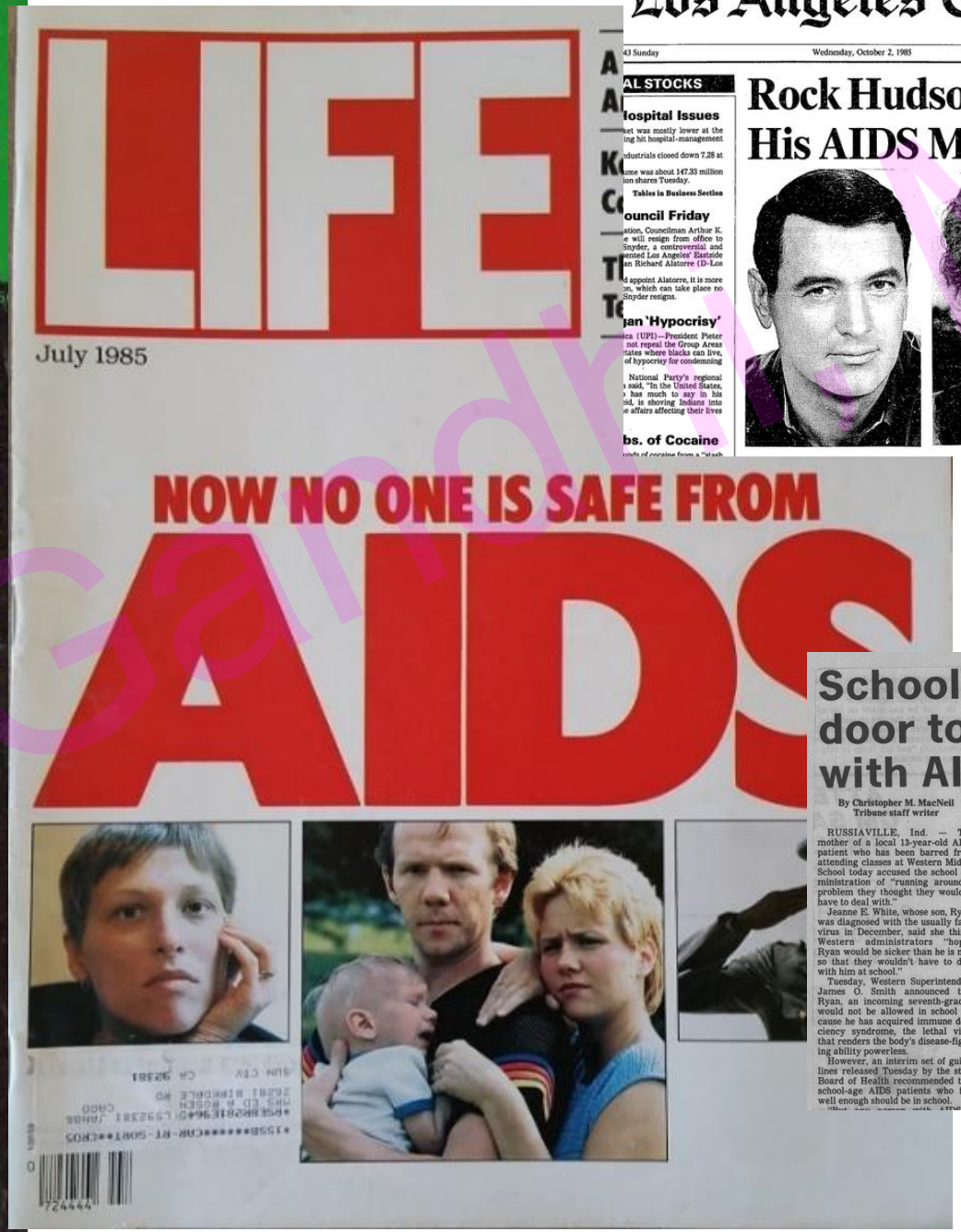
During the past 30 months, Kaposi's sarcoma (KS), an uncommonly reported malignancy in the United States, has been diagnosed in 26 homosexual men (20 in New York City [NYC]; 6 in California). The 26 patients range in age from 26-51 years (mean 39 years). Eight of these patients died (7 in NYC, 1 in California)—all 8 within 24 months after KS was diagnosed. The diagnoses in all 26 cases were based on histopathological examination of skin lesions, lymph nodes, or tumor in other organs. Twenty-five of the 26 patients were white, 1 was black. Presenting complaints from 20 of these patients are

Timeline

- 1981 – MMWR reported 270 of rare immunodeficiency in men, 121 died
- 1982 – GRID labeled AIDS by CDC
- 1983 – Bobbi Campbell AIDS activist appears with his partner (Bobby Hilliard) on cover of *Newsweek*
- 1983 – Virus isolated, antibody test developed
- 1983 – Ward 86 opened doors
- 1984 – Bobbi Campbell died
- 1984 – Bath houses in San Francisco and New York closed
- 1985 – First commercial ELISA approved







1985

NAMES PROJECT

A NATIONAL AIDS MEMORIAL

To date The NAMES Project has received dozens of banners from across the United States. These first panels, which will be sewn together to form the beginnings of the national AIDS quilt, will be displayed at Work of Artz Gallery, 1195 Oak (at Broderick) from Saturday, May 30 and continuing through June.

The NAMES Project Exhibit
WORK OF ARTZ GALLERY
1195 OAK (at Broderick)
SF, CA. 94117
Wed-Fri: 3-7 pm, Sat & Sun 1-6

There will be a Gala Reception and Strawberry Festival to benefit the Project on Sunday, June 14 from 2 to 6 at the Gallery. A donation of $10 will be requested at the door. Anyone bringing a completed memorial panel may attend for $5.

Return to: The NAMES Project, P.O. Box 14573, San Francisco, CA 94114
Please type or print clearly.

NAME _____

ADDRESS _____

1987 – Mike Smith, Cleve Jones, Market Street

October 1987, Washington Mall

Public Domain image

National & International Strategies

- April 8, 1990 – Ryan White, activist, dies at 18
- August 1990- Bipartisan Ryan White Care act passed (150,000 cases, 100,000 deaths in U.S. to date), Eric Goosby MD founding director (1991-5)
  - Few disease specific health programs in the country, charged with serving PLWHA who are low income, un-or underinsured or otherwise lack resources to access services on their own – "wrap-around care"
- 1992 – AIDS leading cause of death U.S. men ages 22-44
- 2003 – PEPFAR program formed
- 2010 –National HIV/AIDS Strategy
- 2019–End the HIV Epidemic initiative

Viewpoint

September 14, 2023

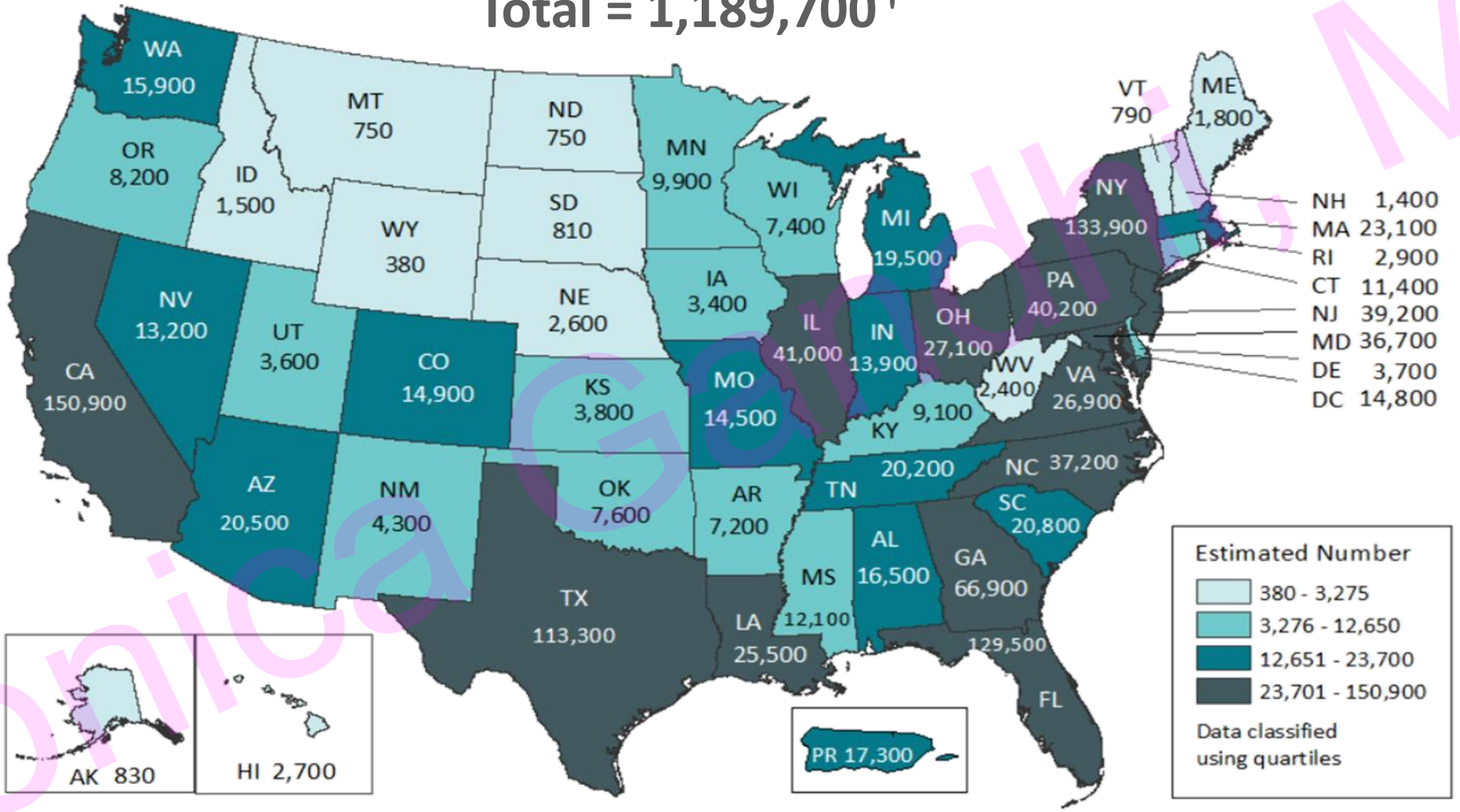
PEPFAR Reauthorization by Congress Urgent for Global Health

Monica Gandhi, MD, MPH[1]; Eric Goosby, MD[2]

JAMA

Estimated HIV Prevalence among Persons Aged ≥13 years, by Area of Residence 2019—United States and Puerto Rico

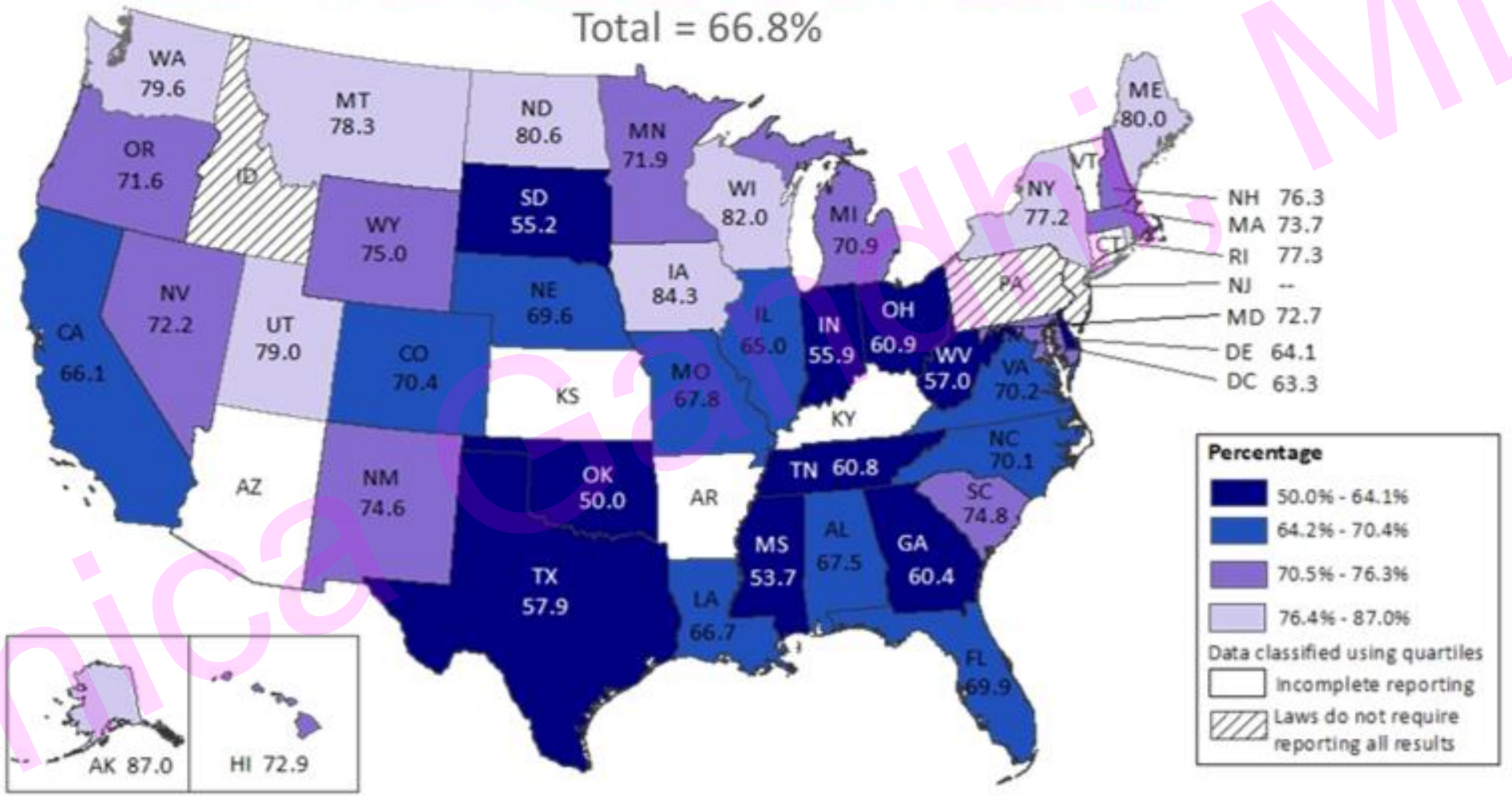
Total = 1,189,700 †



Note. Estimates were derived from a CD4 depletion model using HIV surveillance data. Estimates rounded to the nearest 100 for estimates >1,000 and to the nearest 10 for estimates ≤1,000 to reflect model uncertainty. Estimates for the year 2019 are preliminary and based on deaths reported to CDC through December 2020. Estimates should be interpreted with caution due to incomplete death ascertainment for Kansas, Massachusetts, Mississippi, Nevada, North Dakota, and Vermont.

†Total estimate for the United States does not include data for Puerto Rico.

Viral Suppression within 6 months of Diagnosis among Persons Aged ≥13 Years, 2018—41 States and the District of Columbia



Note. Viral suppression was defined as <200 copies/mL on a VL test within 6 months of HIV diagnosis in 2018. Data are based on residence at diagnosis.

Risks in U.S. cluster with poverty, disease of disparities

- HIV clusters with poverty, interpersonal violence (women), incarceration, 52% new cases in South
- Disparities in new infections (CDC Medical Monitoring Report August 2023)

CDC. Medical Monitoring Project 2023

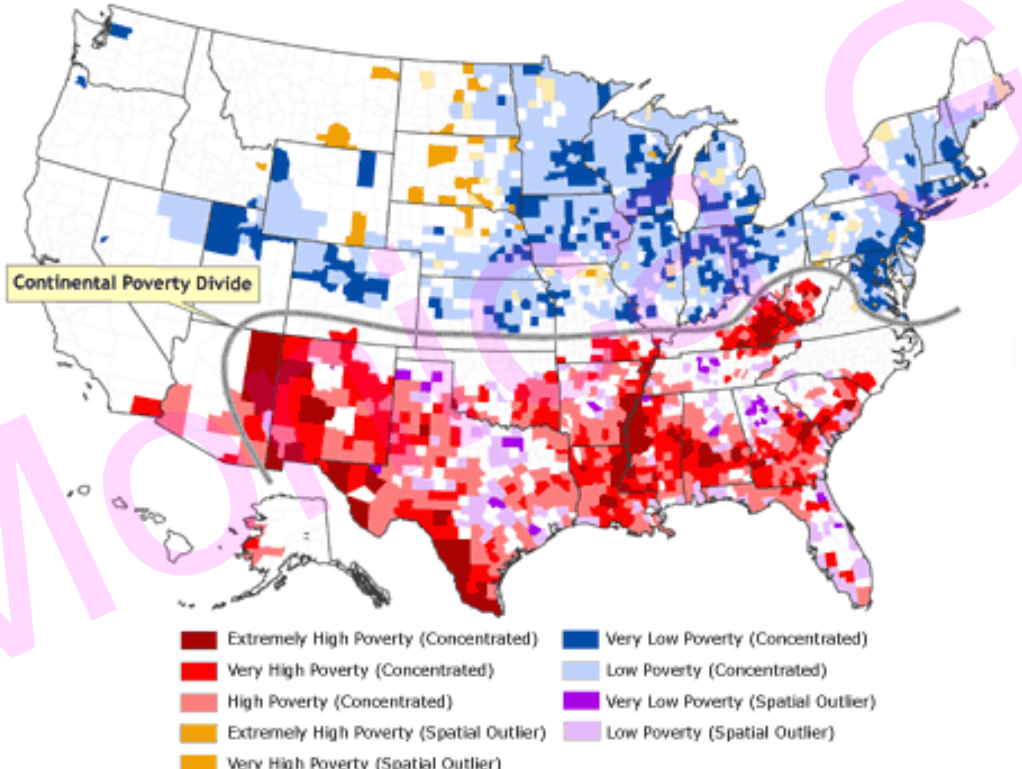
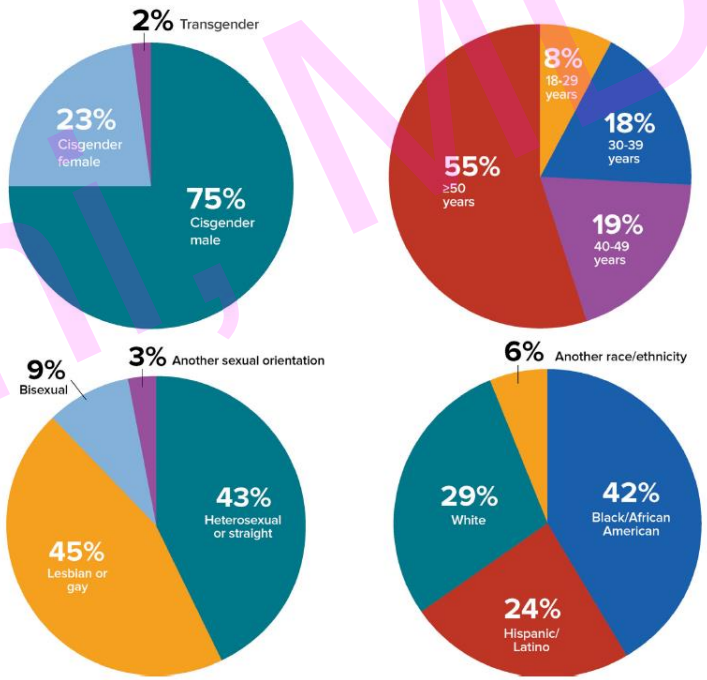
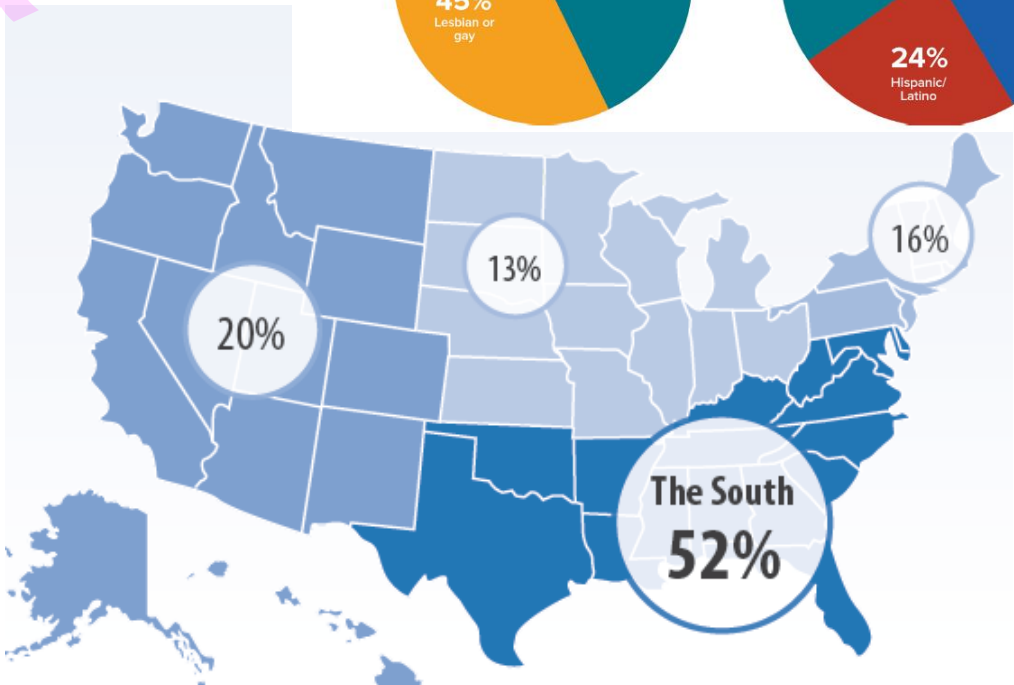


Figure 2. Distribution of gender, age, sexual orientation, and race/ethnicity among adults with diagnosed Medical Monitoring Project, United States, 2020





Timeline of innovative programs at Ward 86 reflect trends in HIV medicine

1983- Present

Investigational Trials

2008 — Women's Clinic

2010 — Universal ART

2013 — RAPID start

2015 — PrEP

2016 — SALUD Clinic- Latino/a

2017 — Golden Compass- HIV & aging

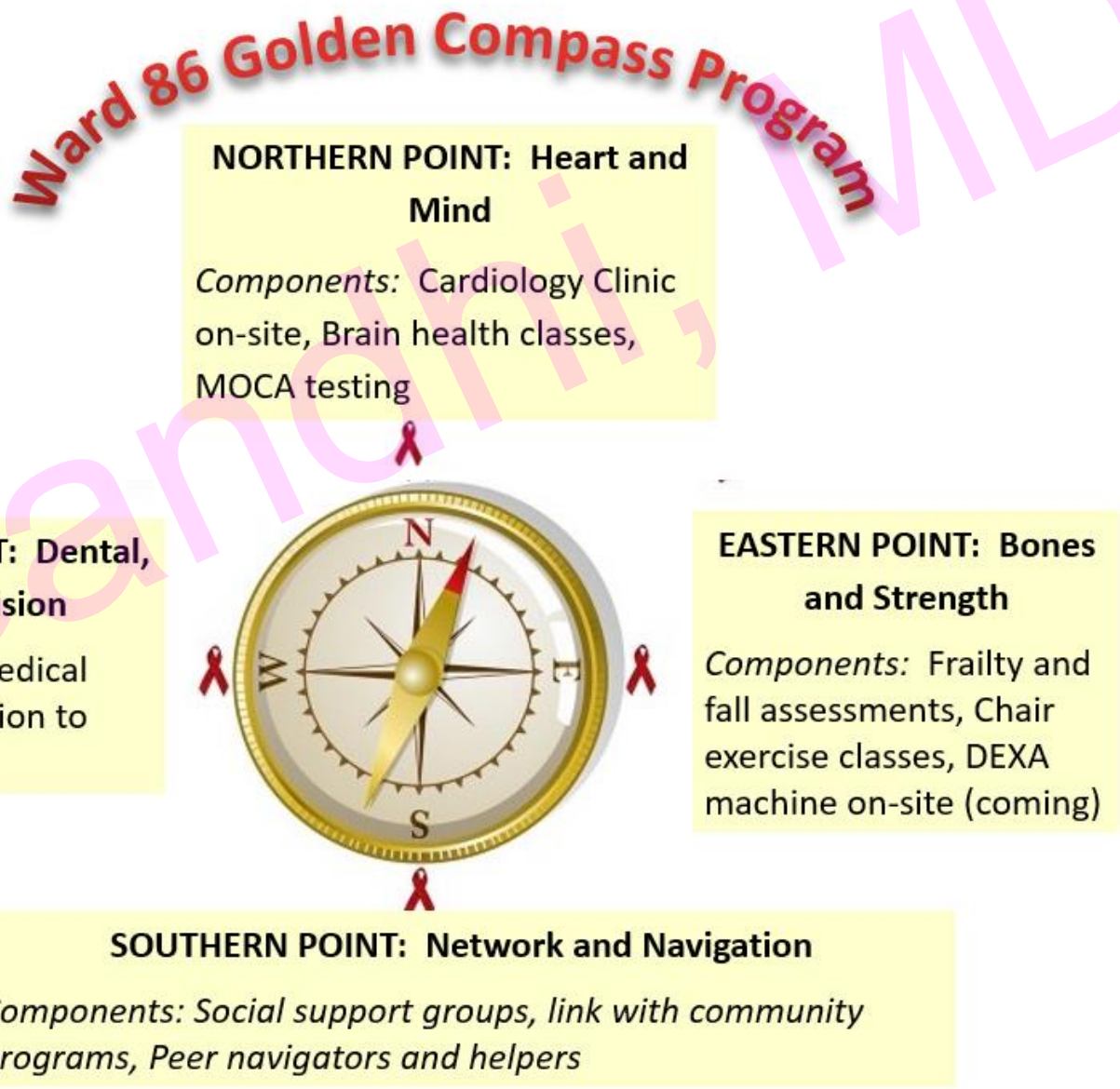
2019 — POP-UI Homeless Clinic

2021 — Ward 86 Special Program on Long-Acting Antiretrovirals to Stop HIV

2023 — Revival of Care program

Golden Compass

- Today, 73 percent of people with *HIV* in *San Francisco* are over the age of 50



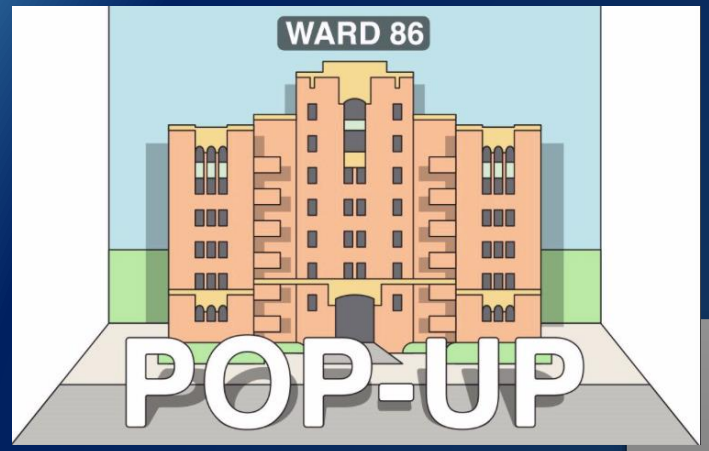
Pop Up Program

75%

Housed persons with HIV in San Francisco are Virally Suppressed

27%

Homeless People with HIV in San Francisco are Virally Suppressed (50-60% in POP-UP)



Provider

RN

Pharmacist

SW

Patient

Medical assistant

Medical services

-ART: Onsite start DOT 5 days a week & counseling
-Health maintenance care (vaccines, STI screening, cancer screening)
-On-site mental health services & buprenorphine initiation

Life services

-Food resources
-Social services (SSI, disability, ADAP, case management referral)
-Emergency housing and treatment program referrals

Revival of care at Ward 86 - 2023

REPRIEVE

Randomized Trial to Prevent Vascular Events in HIV

Clinical Infectious Diseases

MAJOR ARTICLE

Clin Infect Dis. 2023 Sep 12;

Weight gain after antiretroviral therapy initiation and subsequent risk of metabolic and cardiovascular disease

Beyond diet, exercise, control other risk factors for cardiovascular disease; showed a 35% reduction in major adverse CV event among PWH with statin (clearly most important for moderate-high risk groups)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

Steven K. Grinspoon, M.D., Kathleen V. Fitch, M.S.N., Markella V. Zanni, M.D., Carl J. Fichtenbaum, M.D., Triin Umbleja, M.S., Judith A. Aberg, M.D., Edgar T. Overton, M.D., Carlos D. Malvestutto, M.D., M.P.H., Gerald S. Bloomfield, M.D., M.P.H., Judith S. Currier, M.D., Esteban Martinez, M.D., Ph.D., Jhoanna C. Roa, M.D., Marissa R. Diggs, B.A., Evelynne S. Fulda, B.A., Kayla Paradis, M.B.A., Stephen D. Wiviott, M.D., Borek Foldyna, M.D., Sara E. Looby, Ph.D., Patrice Desvigne-Nickens, M.D., Beverly Alston-Smith, M.D., Jorge Leon-Cruz, M.S., Sara McCallum, M.P.H., Udo Hoffmann, M.D., M.P.H., Michael T. Lu, M.D., M.P.H., Heather J. Ribaudo, Ph.D., and Pamela S. Douglas, M.D., for the REPRIEVE Investigators*

ABSTRACT

Participants who experienced >10% weight gain in 1st year of ART had an increased risk of DM (HR 2.01), metabolic syndrome (HR 2.24), and cardiometabolic outcomes (HR 1.54)

BIGGEST UPDATES IN TREATMENT 2023

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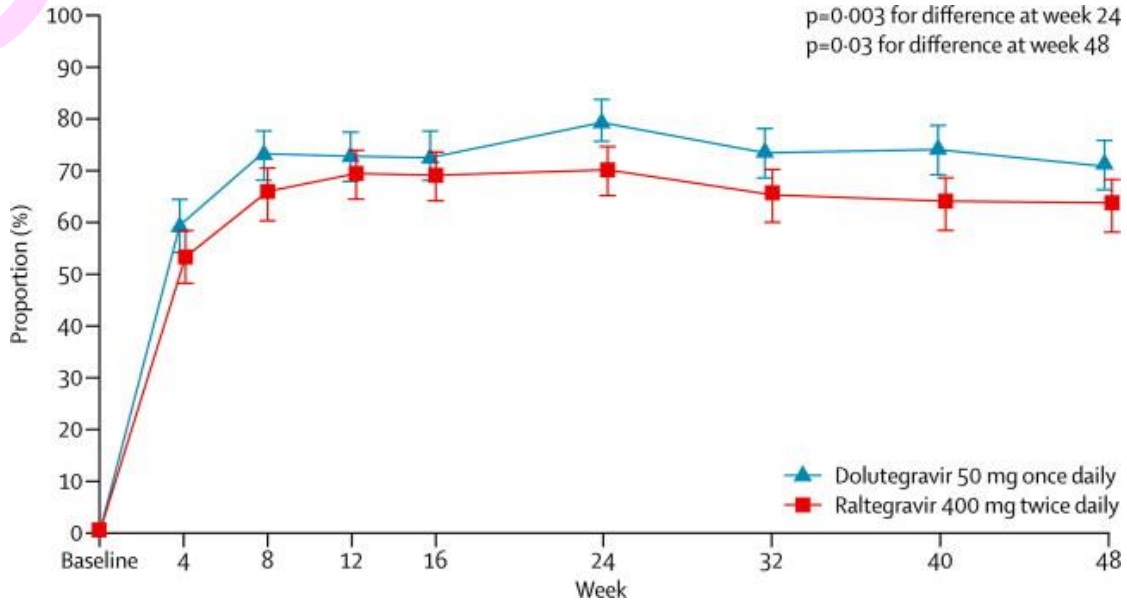
INSTIs FIRST-LINE AT THIS POINT FROM NAÏVE/SWITCH TRIALS WITHOUT RESISTANCE

Study	Population	Comparator	Outcome	Resistance
BICTEGRAVIR				
1489	Naïve	DTG/ABC/3TC	Non-inferior	0
1490	Naïve	DTG+FTC/TAF	Non-inferior	0
1844	Suppressed	DTG/ABC/3TC	Non-inferior	0
1878	Suppressed	Boosted PI + 2 NRTIs	Non-inferior	0 to INSTI but 1 L74V in PI arm
1961 (women)	Suppressed	E/C/F/(TAF or TDF) ATV+RTV + FTC/TDF	Non-inferior	0 to INSTI but 1 M184V in ELV/cobi
DOLUTEGRAVIR				
SINGLE	Naïve	EFV/TDF/FTC	Superior	0 in DTG arm; 7 in EFV
FLAMINGO	Naïve	DRV/r with 2 NRTI backbone	Superior	0 in either
SPRING-2	Naïve	RAL with 2 NRTI backbone	Non-inferior	0 in DTG; 1 INSTI/NRTI in RAL

Accumulating data for INSTIS as 2ND line in face of resistance

- SAILING STUDY –PI, NNRTI AND /OR NNRTI RESISTANCE
- Dolutegravir 50mg po daily vs Raltegravir 400mg po BID in patients with resistance to ≥ 2 classes of antiretrovirals with 1-2 remaining active agents for background therapy
- Investigator chosen background
- DTG was SUPERIOR to RTG in virologic suppression at week 48 and no development of resistance



71%

64%

Cahn P. Lancet 2013. 382(9893):700-8

VIKING Study: DTG in setting of NRTI, NNRTI, PI, and INSTI resistance

- Dolutegravir 50mg po **BID** vs placebo in patients with resistance to ≥ 2 classes including INSTIs (resistance to raltegravir or elvitegravir) – should have 1 other active drug
- Investigator chosen background
- DTG resulted in 53% virologic suppression (<400)
- Participants with Q148 with 2 other INSTI mutations don't have activity

Remember to double the dose of dolutegravir to 50mg po BID

Table 2. Comparison of DTG 50 mg twice daily versus PCB for change in BL HIV-1 at day 8 and antiviral efficacy of open-label DTG 50 mg twice daily with OBR at weeks 24 and 48 by BL characteristics[a]

	DTG 50 mg twice daily change from BL[b] at day 8[a] (*n*=14)		PCB 50 mg twice daily change from BL[b] at day 8[a] (*n*=16)		Combined arms, HIV-1 RNA <50 copies/ml[a] (%) (*n*=30)	
Subgroup	*n*	Mean (SD)	*n*	Mean (SD)	Week 24	Week 48
Overall[c]	14[d]	-1.06 (0.17)	16	0.10 (0.18)	14/30 (47)	12/30 (40)
DTG FC						
0–2.5	4	-1.33 (0.82)	7	0.00 (0.34)	6/11 (55)	5/11 (45)
>2.5–4	2	-1.22 (0.65)	3	-0.13 (0.28)	3/5 (60)	3/5 (60)
>4–8	5	-0.89 (0.65)	4	-0.02 (0.22)	2/9 (22)	1/9 (11)
>10–20	1	-0.86	1	-0.06	1/2 (50)	1/2 (50)
>20	1	-0.16	1	0.09	1/2 (50)	1/2 (50)
Missing	1	-1.82	0		1/1 (100)	1/1 (100)
Derived IN mutation group						
No Q148[e]	5	-1.43 (0.745)	9	-0.03 (0.325)	9/14 (64)	8/14 (57)
Q148 +1[f]	6	-0.87 (0.587)	6	-0.05 (0.182)	4/12 (33)	3/12 (25)
Q148 +≥2[f]	3	-0.90 (0.758)	1	0.09	1/4 (25)	1/4 (25)
OSS[g] of background ART						
0	–	–	–	–	2/3 (67)	2/3 (67)
1	–	–	–	–	6/15 (40)	5/15 (33)
2	–	–	–	–	3/8 (38)	3/8 (38)
>2	–	–	–	–	3/4 (75)	2/4 (50)

Bisher A. Antivir Ther. 2015;20(3):343-8

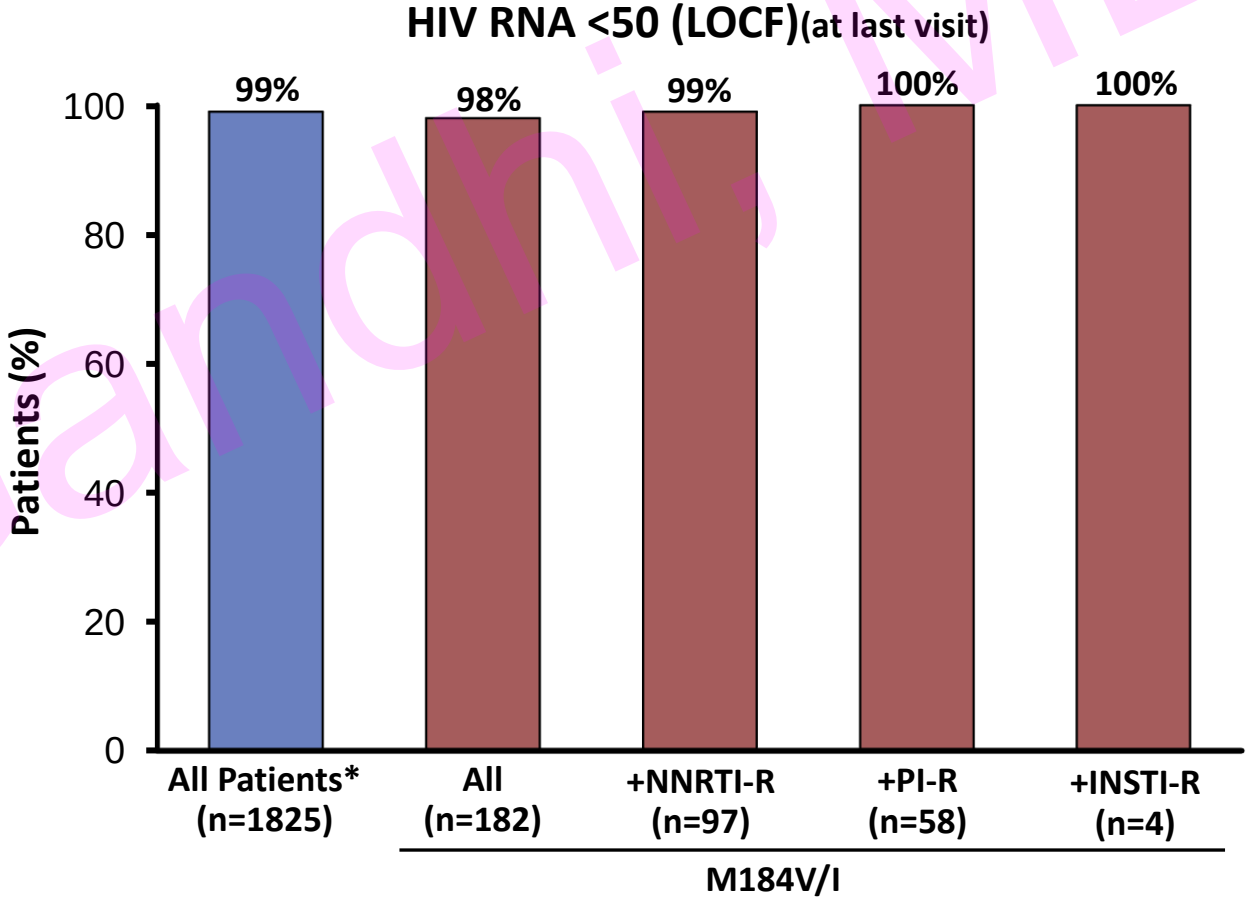
Recent studies of DTG with NRTI resistance

Name of study	Type of study, n	Comparison	Outcome	Emergent resistance
DAWNING	Open-label noninferiority study in PWH failing 1st line NNRTI + 2 NRTIs, n=624	DTG + 2NRTIs vs LPV/RTV + 2 NRTIs	DTG superior to LPV/RTV in subgroups	2 patients failed with INSTI resistance; none with PI resistance
NADIA	Switch study in PWH failing NNRTI/TDF/3TC (86% M184V; 50% K65R), n=464	DTG or DRV/r with either TDF/3TC or AZT/3TC	DTG + 2 NRTIs noninferior to DRV/r + 2 NRTIs (TDF/FTC works well even if resistance predicted)	9 patients in DTG arm failed with resistance; none in DRV/r arm
VISEND	Open-label study randomized PWH failing NNRTI-based therapy, n=1201	DTG or boosted PI regimens	>80% virologic suppression (<50) on DTG regimens	None reported (abstract CROI 2022)
2SD	Randomized study 2nd line therapy, Kenya, n=795	PI/r + 2 NRTIs randomized switch to DTG + 2 NRTI or continue	>90% virologic suppression each arm	No emergent resistance either arm

DAWNING: Aboud M, et al. *Lancet Infect Dis*. 2019**; NADIA:** Patton N. Lancet HIV 2022; **VISEND**: Mulenga LB, et al. CROI 2022. Abstract 135; **2SD Study**: Ombajo L N Engl J Med 2023 Jun 22;388

Bictegravir/FTC/TAF with suppressed HIV and pre-existing M184V/I

- Pooled data from 6 trials in which PWH and virologic suppression switched to B/F/TAF (n=1825 with baseline data)
- Preexisting M184V/I identified in 182 participants (10%)
- 98% of participants with pre-existing M184V/I maintained viral suppression

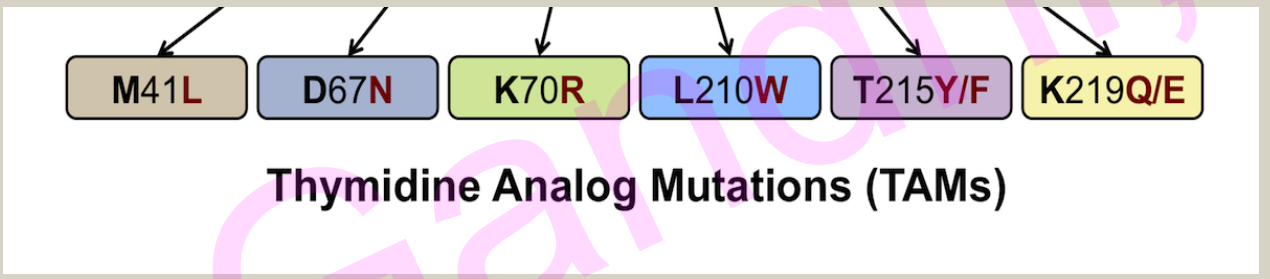


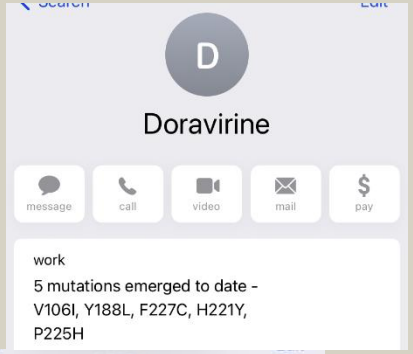
LOCF: last observation carried forward.
*Patients with baseline data.

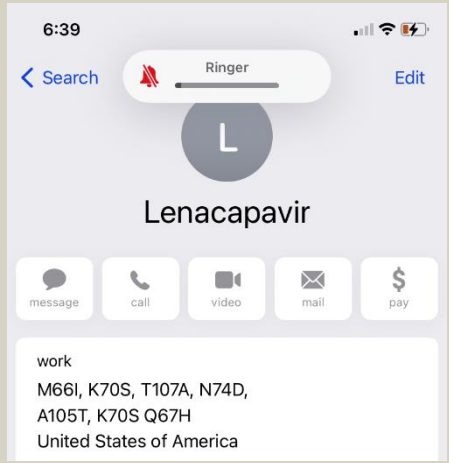
Sax PE, et al. *AIDS*. 2022

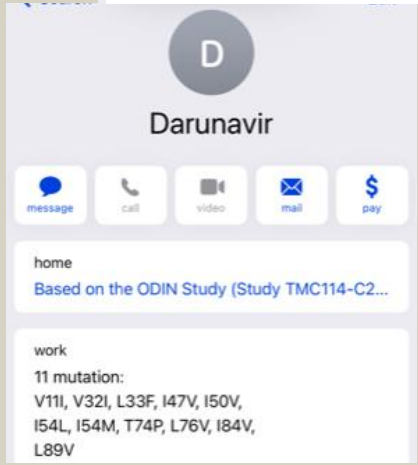
The 12 mutations every HIV provider should know

- **NRTI**
  - **M184V (3TC), K65R (TDF), L74V (ABC)**
  - 6 Thymidine-associated mutations (TAMs) - **M41L, D67N, K70R, L210W, T215Y/F, K219Q**
- **NNRTI**
  - **K103N** (EFV, NVP)
  - **Y181C** (ETR)
  - **E138K** (RPV)
  - I will send you Doravirine contact
- **PI**
  - None
- **INSTI**
  - Know Q148H for DTG and R263K with BIC
- **Capsid inhibitor**
  - None







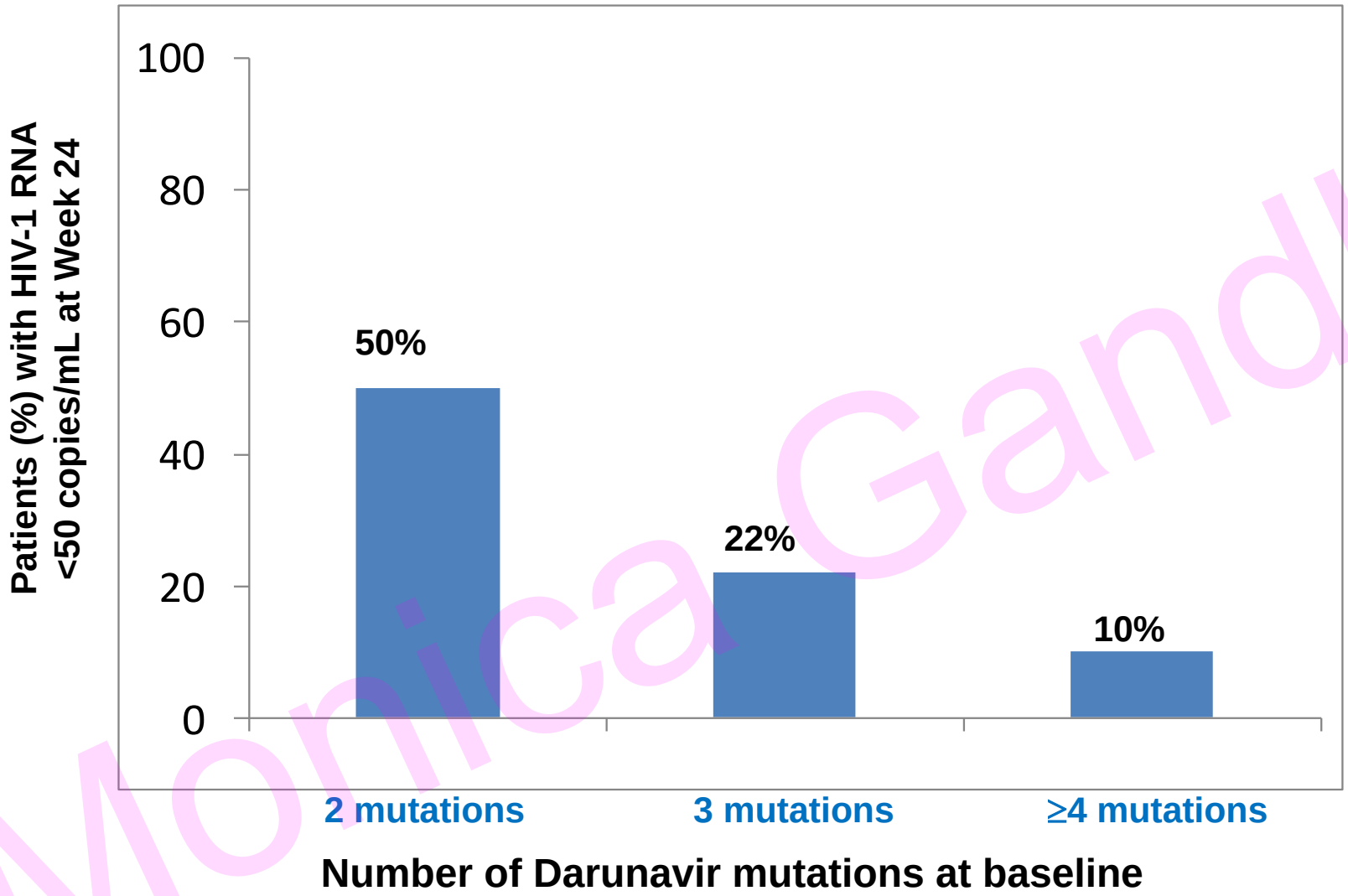


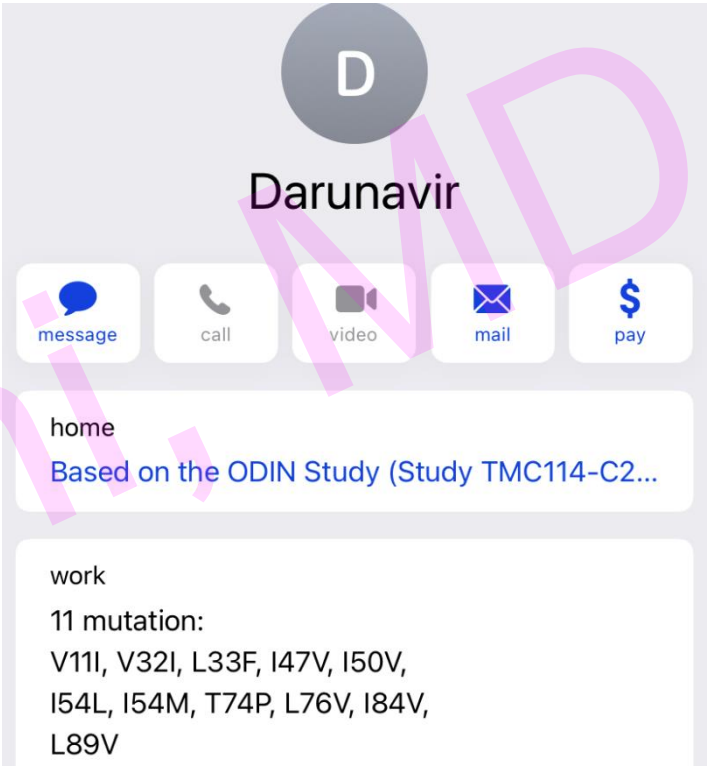
DHHS Guidelines available at http://aidsinfo.nih.gov/guidelines

What are the four drugs we can use for multidrug resistant HIV?

1. TDF, T20, bNAbs
2. Boosted darunavir, T20, Delavirdine
3. Maraviroc, Fostemsavir, Ibalizumab, Lenacapavir
4. Boosted lopinavir, boosted tipranavir, TDF

Darunavir response by DRV score





If you text me, I will send you the darunavir contact!

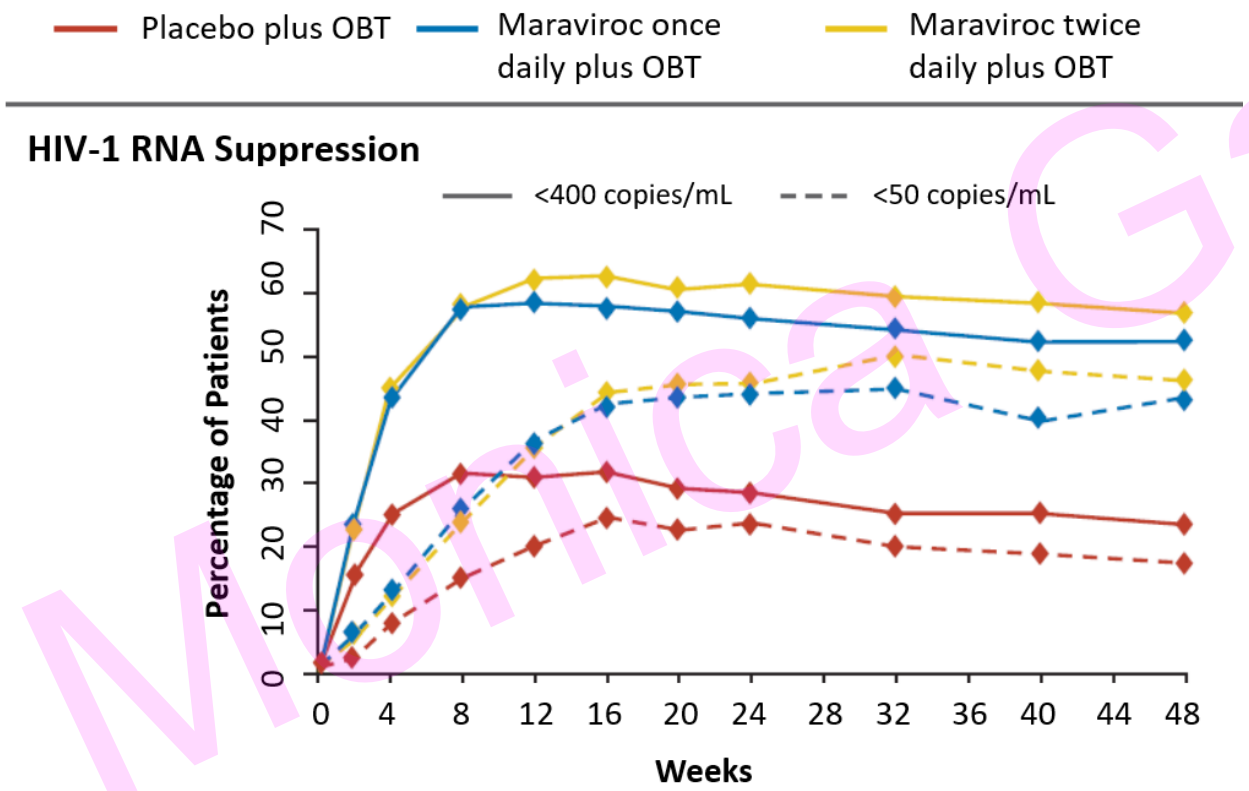
Use BID (twice daily DRV/r) if have 2-3 mutations and efficacy really falls off after 4 or more mutations

De Meyer S, et al. Resistance Workshop 2006. Abstract 73.; Levin J et al, XVIII Intl Drug Resistance Workshop, June 9-13, 2009.

Maraviroc for MDR patients with viremia: MOTIVATE-1 and -2 studies

CCR5 receptor antagonist approved in 2007 for patients with CCR5-tropic, multidrug-resistant HIV

Parallel phase studies of viremic MDR patients (N = 1,049) on optimized background therapy (OBT) per treatment history and resistance testing, randomized to additionally receive maraviroc daily, maraviroc BID, or placebo

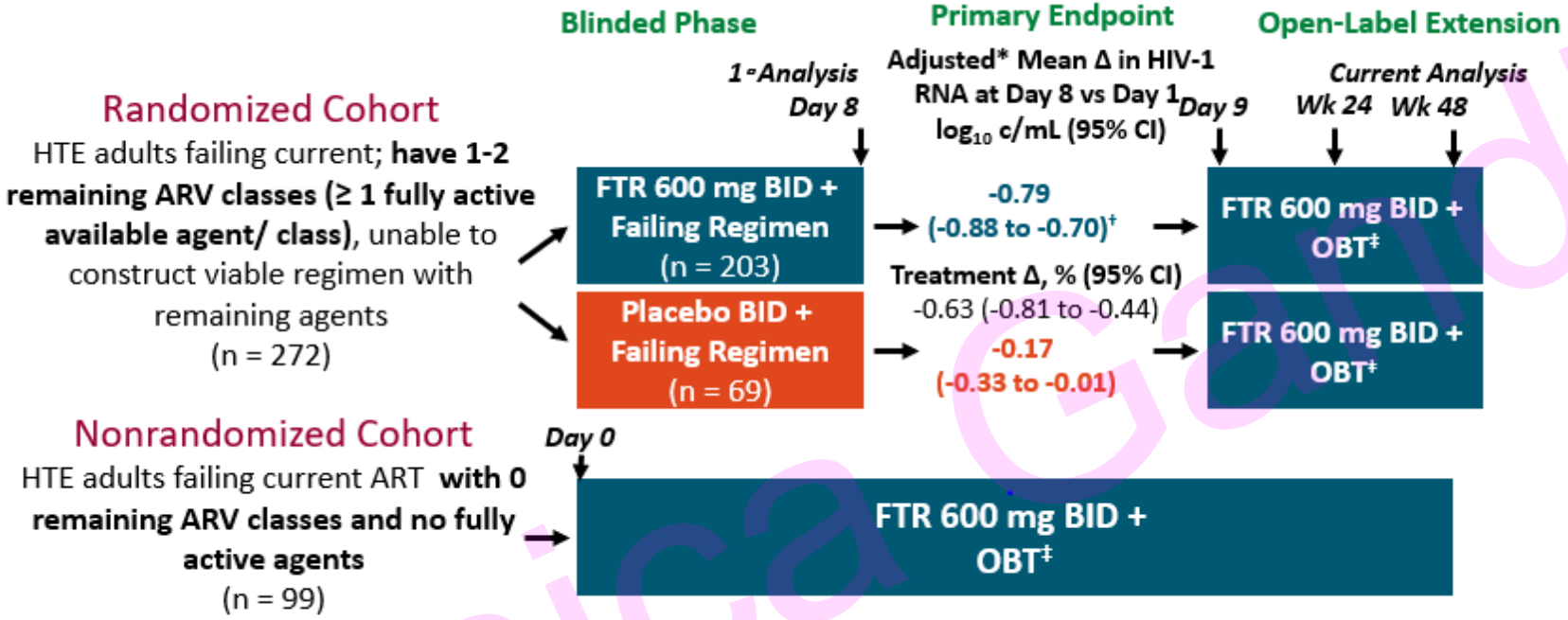


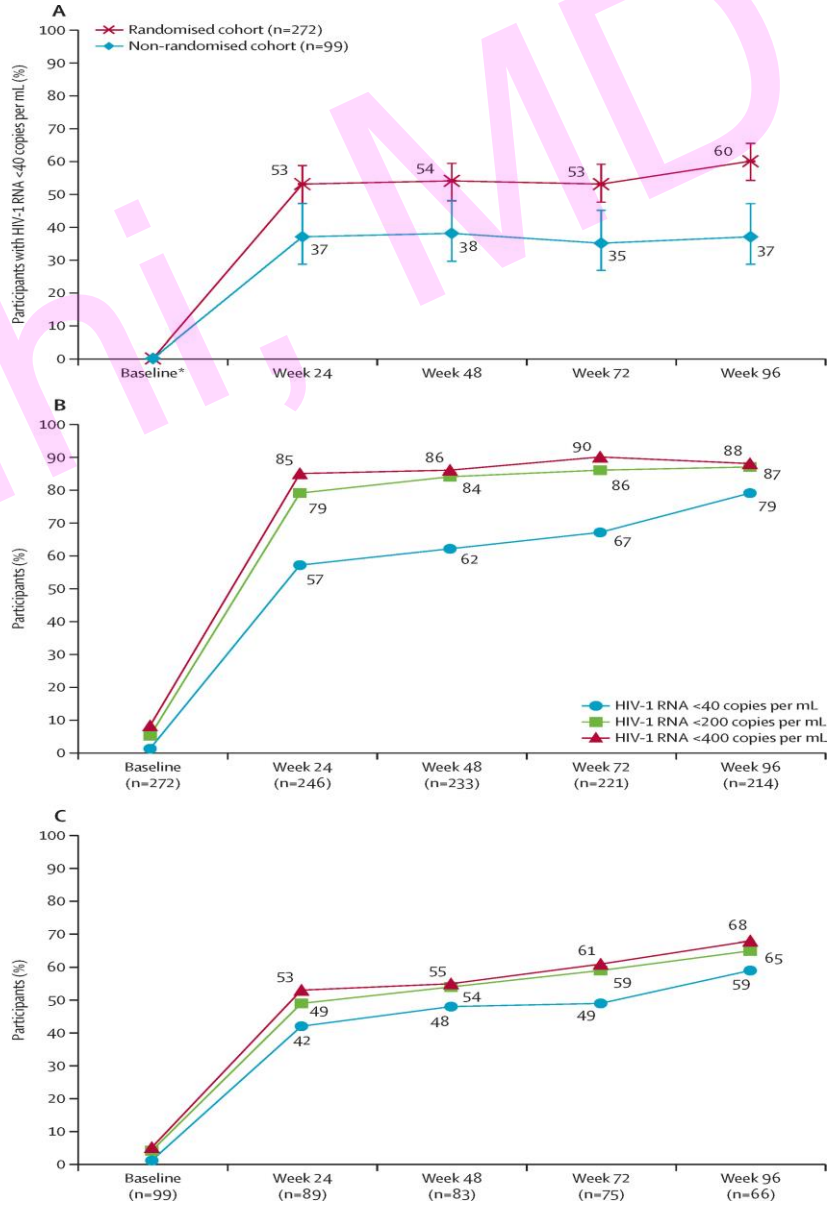
Must assess CCR5 tropism prior to using this medication

Adding maraviroc to OBT was associated with improved viral suppression

OBT = Optimized Background Regimen; MVC = Maraviroc; BID = Twice Daily; **Gulick RM, et al. *N Engl J Med*. 2008;359(14): 1429-1441.**

BRIGHTE: Fostemsavir in Heavily Treatment–Experienced Adults at Wk 96





Metabolized into temsavir which binds to viral glycoprotein 120, preventing binding to CD4 (600mg po BID, no major ddIs)

Latallaide Lancet HIV 2020.

Ibalizumab: IV (now 30 second push) Option for MDR HIV

Guernica –
Pablo Picasso

Given every 2 weeks in addition to optimized background regimen in MDR HIV failing ART
Administered via intravenous infusion or 30-second IV push (IV push approved Oct 2022)

Phase 3 TMB-301 Efficacy Results:

% of participants with HIV RNA < 50 c/mL

- **Week 24: 43%**
- **Week 48: 59%**

Efficacy Results from TMB-311 Expanded Access Protocol (N = 38):

% of participants with HIV RNA < 50 c/mL

- **Week 24: 46%**
- **Week 48: 47%**
- **Week 96: 55%**

CD4-directed (gp120) post-attachment inhibitor approved in 2018

HTE = Heavily Treatment-Experienced; MDR = Multidrug-Resistant; ART = Antiretroviral Therapy

Emu B, et al. *New Engl J Med*. 2018;379(7):645–654; Emu B, et al. IDWeek 2019. Washington, DC. Abstract 661; Emu B, et al. CROI 2019. Seattle, WA. Abstract 485; Towner W, et al. IDWeek 2020. Abstract 1027.

LEN Targets Multiple Stages of HIV Replication Cycle

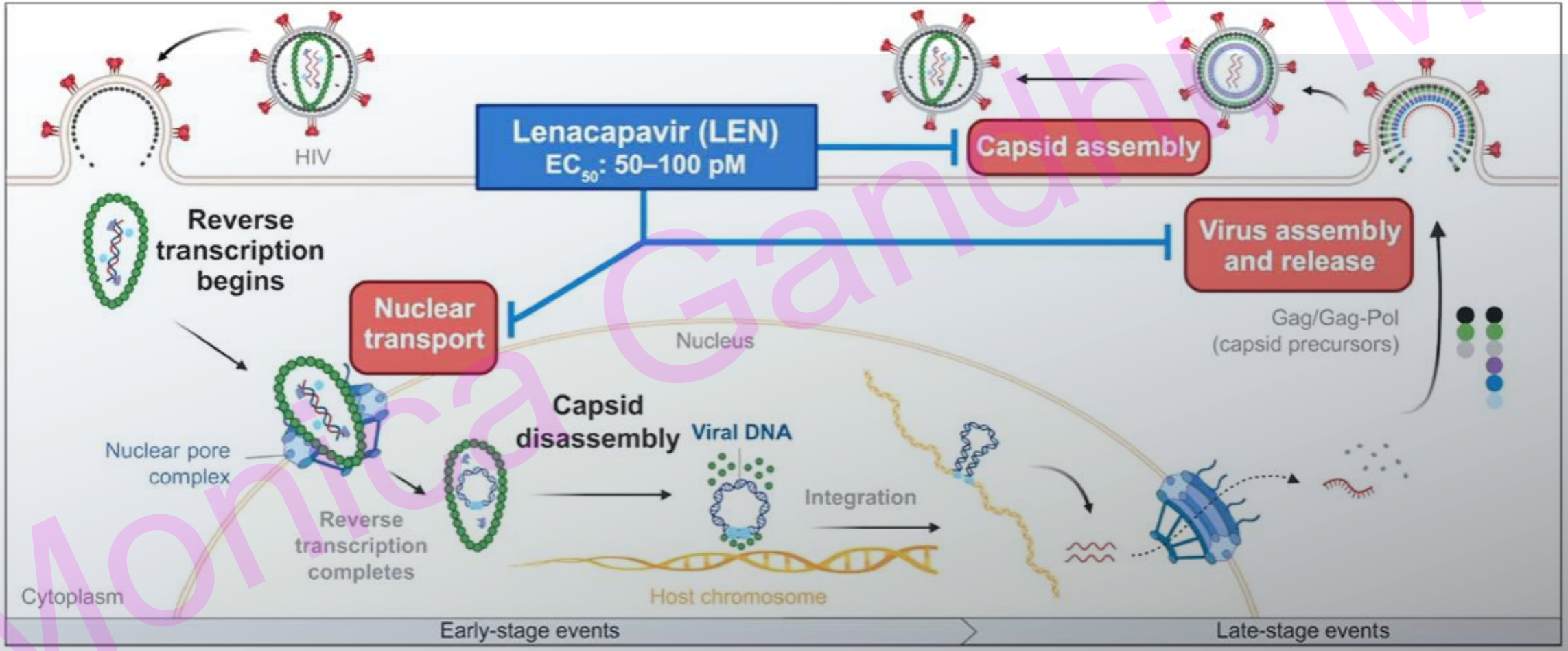
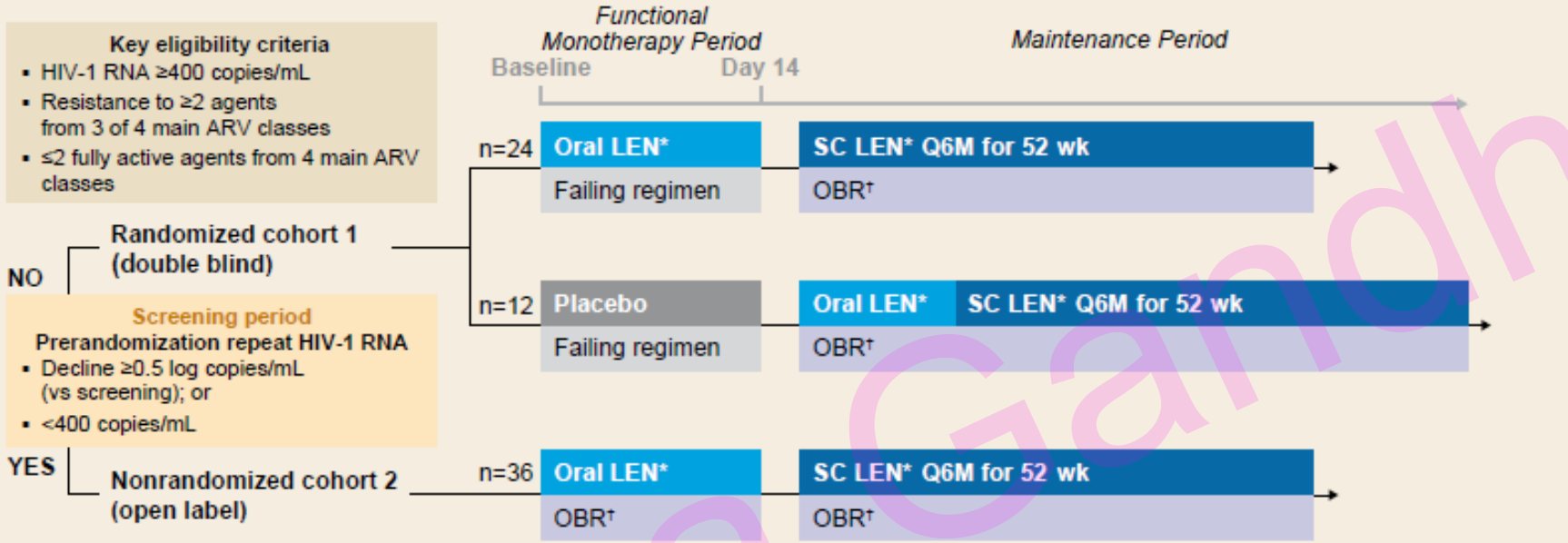
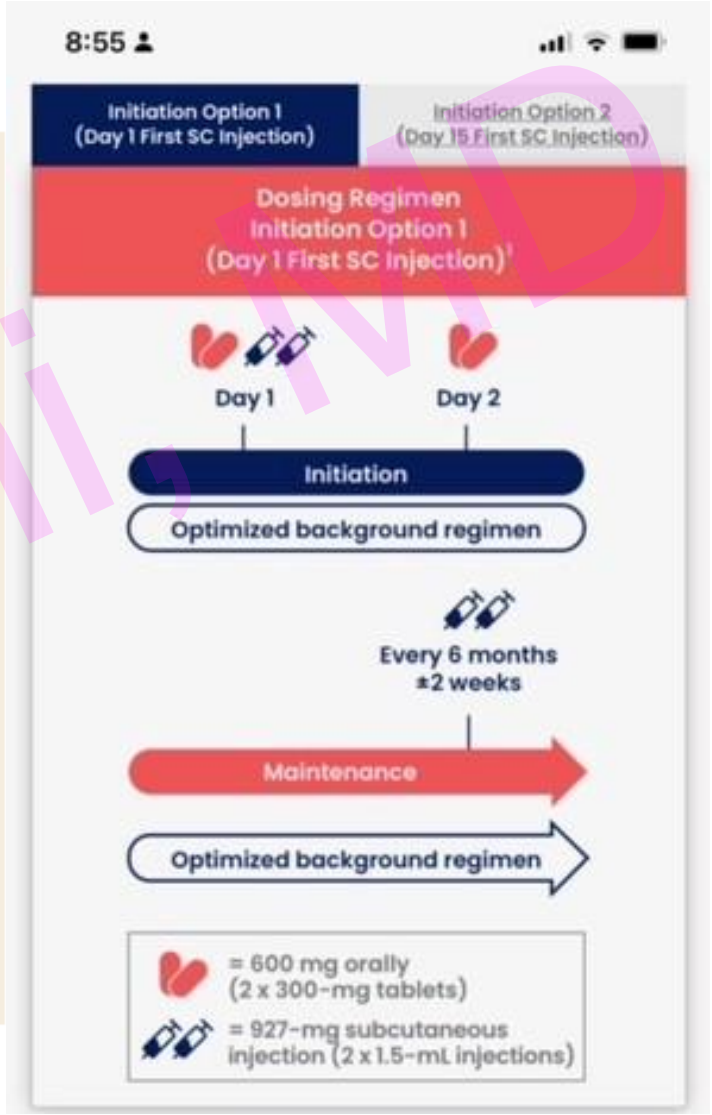


FIGURE 1. Lenacapavir targets multiple stages of the HIV replication cycle. Adapted from [4&&,5].

CAPELLA Study Design[9-11]



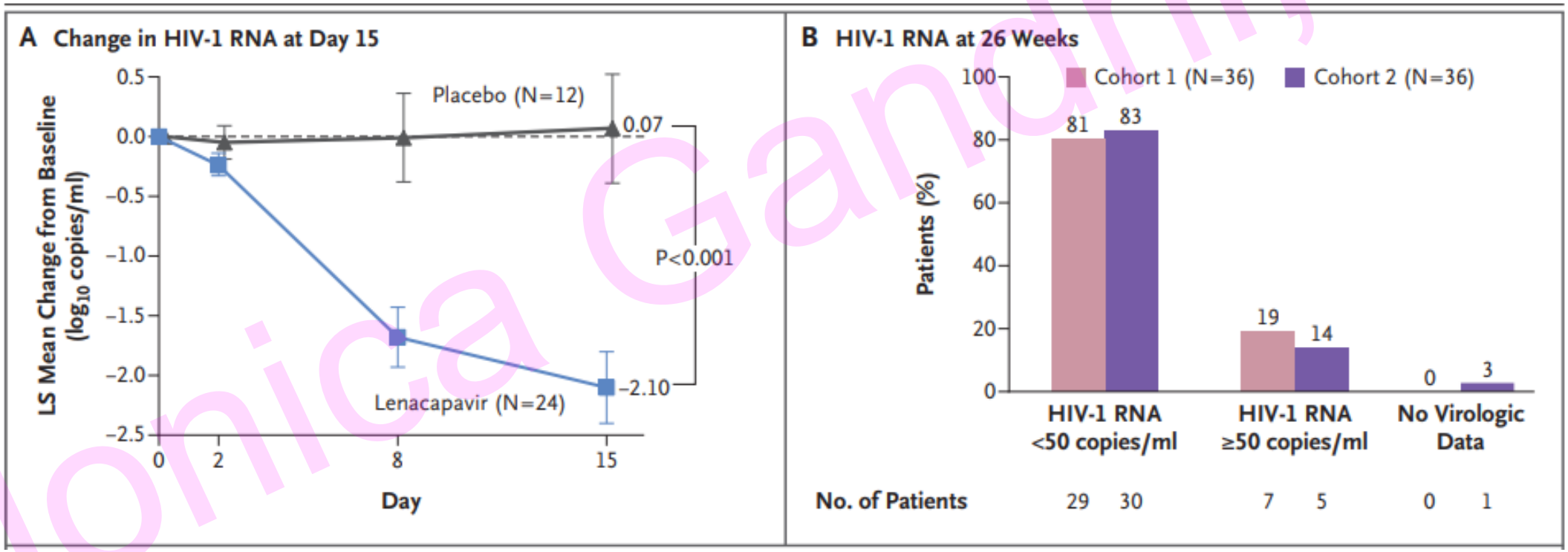
*Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8 (600 mg on Days 15 and 16, and 300 mg on Day 22 for placebo participants); SC LEN administered as 927 mg (2 x 1.5 mL) in abdomen on Day 15; †Investigational agents, such as fostemsavir (FTR), were allowed; atazanavir (ATV), ATV/cobicistat (c), ATV/ritonavir (r), efavirenz, entecavir, nevirapine, and tipranavir were not allowed.



Oral loading dose given days 1, 2 and 8 in CAPELLA but further PK study showed only 600mg (300mg x 2) on days 1 and 2 needed (package insert); then 927mg sq injection (two 1.5ml) q26 weeks (Jogiraju. PK study. AIDS 2022)

CAPELLA STUDY- Lenacapavir in MDR HIV

Approved for MDR HIV now in Europe and in the US since December 2022



Segal Maurer NEJM 2022

Bottom line on LEN resistance in MDR study

Phase 2/3: LEN in HTE PLWH

LEN in HTE ‡

Capella

Postbaseline Resistance Analysis at Week 52

Resistance category, n (%)	Randomized cohort n = 36	Nonrandomized cohort n = 36	Total N = 72
Resistance analysis population	11 (31)	11 (31)	22 (31)
With data	11 (31)	10 (28)	21 (29)
With LEN resistance	4 (11)	5 (14)	9 (13)
M66I, n	4	2	6
Q67H/K/N, n	1	3	4
K70H/N/R/S, n	1	3	4
N74D, n	3	0	3
A105S/T, n	3	1	4
T107A/C/N, n*	1	3	4

- Since Week 26, one additional participant had emergent LEN resistance at Week 52 (*Q67H*)
- All 9 participants with emergent LEN resistance were at high risk for resistance development
  - 4 had no fully active drugs in OBR
  - 5 had inadequate adherence to OBR
- All 9 remained on LEN
  - 4 participants resuppressed at a later visit (2 without OBR change and 2 with OBR change)
- The most common pattern was *M66I* ± other mutations (median LEN fold change was 234)

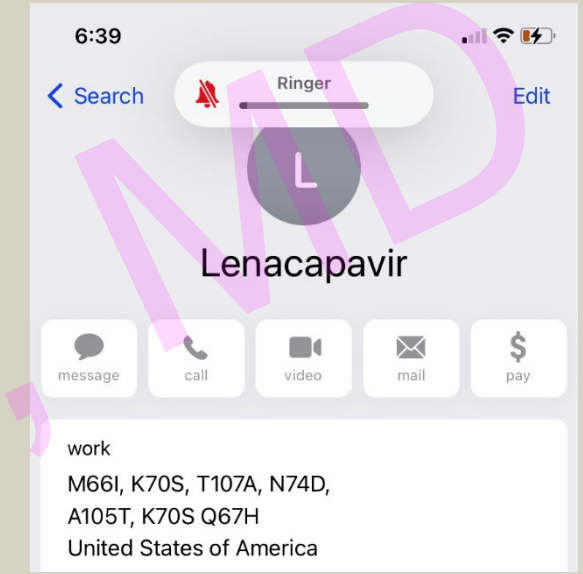
All nine cases of emergent LEN resistance occurred in the setting of functional monotherapy. More than half of participants who met criteria for resistance testing did not develop LEN resistance

*1 participant had emergent *T107A* mutation in capsid, with no loss in LEN susceptibility before achieving HIV -1 RNA suppression; the participant was not categorized as having emergent capsid resistance. HTE, heavily treatment-experienced; OBR, optimized background regimen

Ogbuagu O, et al. IDWeek 2022, Oral 1585

20

External Use-Do Not Distribute



- Mutations to put into your phone contact: M66I, K70S, T107A, N74D, A105T, K70S, Q67H
- All 9 out of 72 occurred during "functional" monotherapy – not having support of OBR

What was the first data suggesting INSTIs are linked with weight gain? (CROI 2019)

Bourgi K et al. *Journal of the International AIDS Society* 2020, **23**:e25484
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25484/full | https://doi.org/10.1002/jia2.25484

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

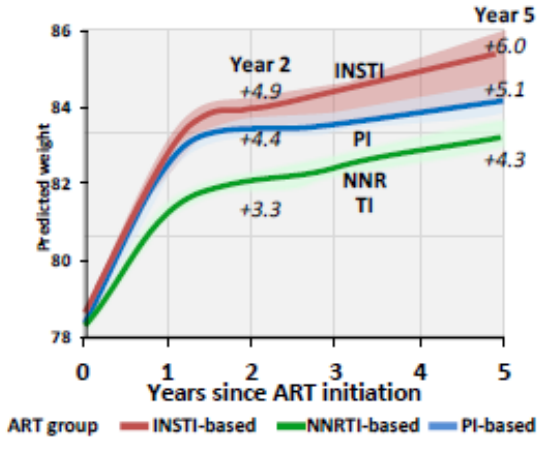
RESEARCH ARTICLE

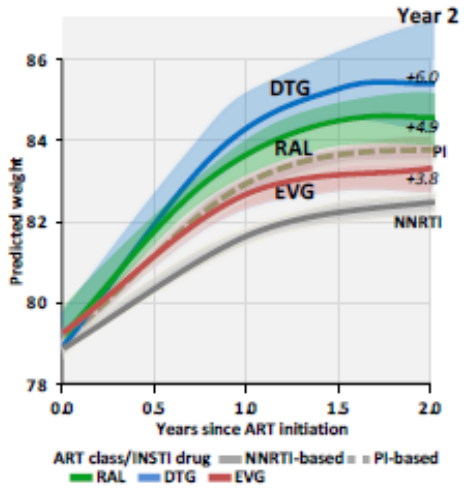
Weight gain among treatment-naïve persons with HIV starting integrase inhibitors compared to non-nucleoside reverse transcriptase inhibitors or protease inhibitors in a large observational cohort in the United States and Canada

Kassem Bourgi[1,2], Cathy A Jenkins[1], Peter F Rebeiro[1], Bryan E. Shepherd[1], Frank Palella[3], Richard D Moore[4],

Weight Gain and Integrase Inhibitors

- NA-ACCORD: observational study of 24,001 participants initiating ART
  - INSTIs, PIs associated with greater weight increase than NNRTI
  - DTG and RAL associated with greater weight gain than EVG

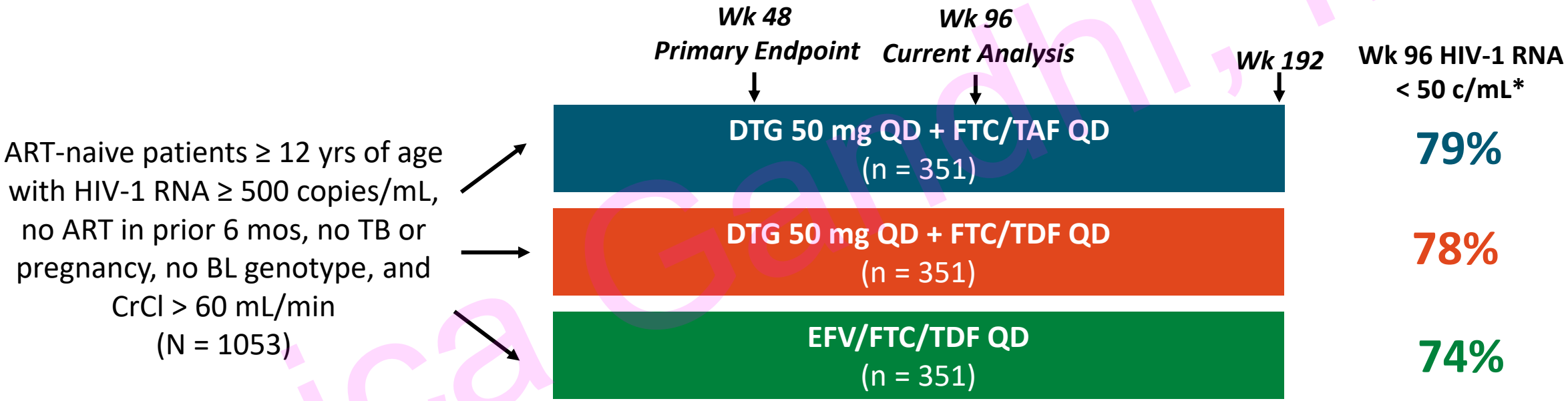




Bourgi K et al, CROI 2019, #670

ADVANCE: Phase III Trial of First-line DTG + FTC/(TAF or TDF) vs EFV/FTC/TDF in South Africa

- Multicenter, randomized, open-label phase III trial conducted in South Africa



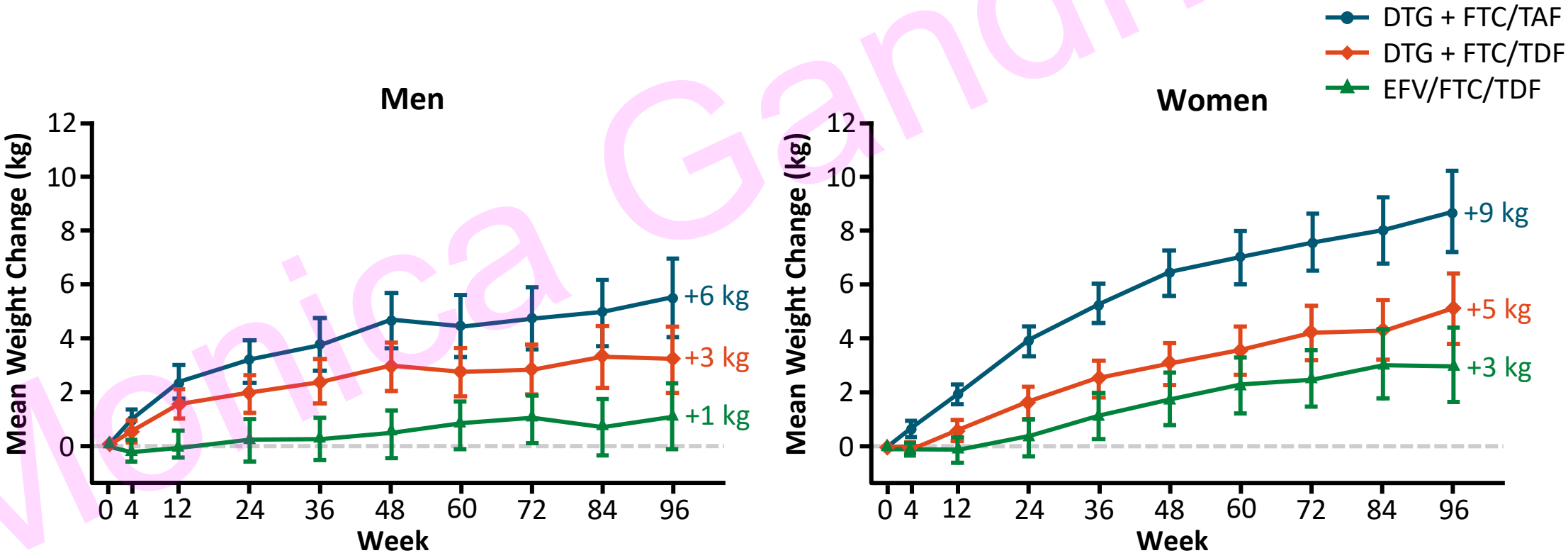
*Differences between arms not statistically significant.

- Primary efficacy endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 by ITT (M = F) analysis
  - DTG + FTC/TAF and DTG + FTC/TDF noninferior to EFV/FTC/TDF at Wk 48: 84% vs 85% vs 79%
- Secondary endpoints: safety, weight gain

Sokhela. AIDS 2020. Abstr OAXLB01. Venter. NEJM. 2019;381:803.

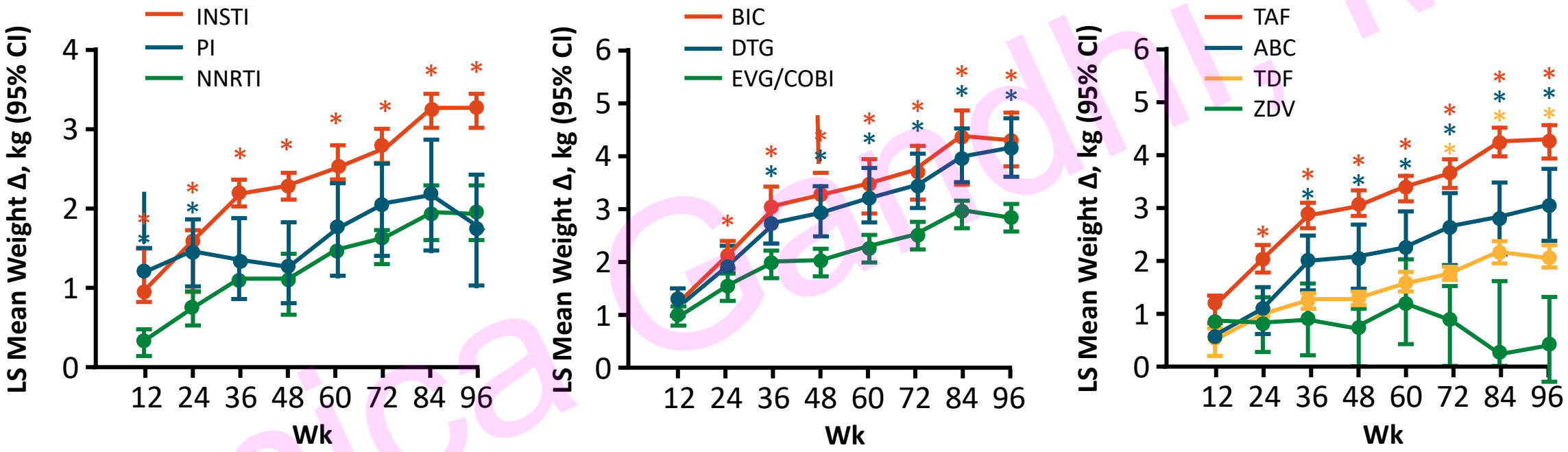
ADVANCE: Mean weight change by up to 96 weeks

- Greater weight increase with DTG vs EFV, with TAF vs TDF; plateau in weight gain after Week 48 observed in men but not in women
  - Same patterns observed for percentage change in weight and change in BMI category over time



McCann. EACS 2019. Abstr PS3/3. Venter. NEJM. 2019;381:803.

Weight gain following ART initiation by ARV class and ARV drug: BIC, DTG, TAF

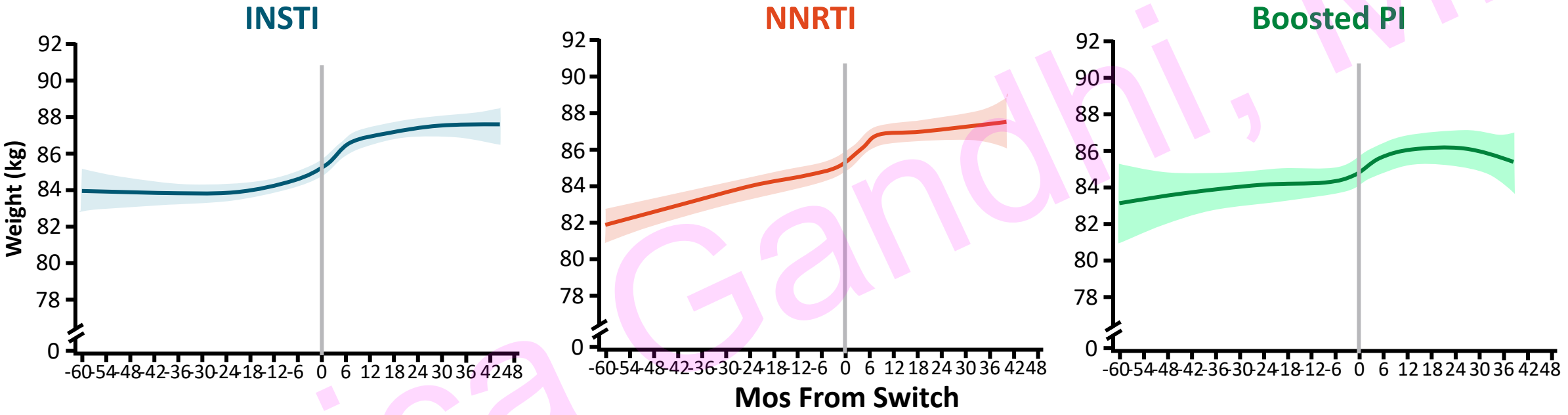


*8 RCTs of PWH treatment-naïve initiating ART between 2003 and 2015, >5000 participants & 10 000 person-years of follow-up

Color-coded to match respective comparators, denoting $P \leq .05$ vs NNRTI (first panel), EVG/COBI (second panel), or ZDV (last panel).

Sax. Clin Infect Dis. 2020;71:1379.

OPERA: Weight change with switch from TDF to TAF (maintain anchor so this is just about TAF)

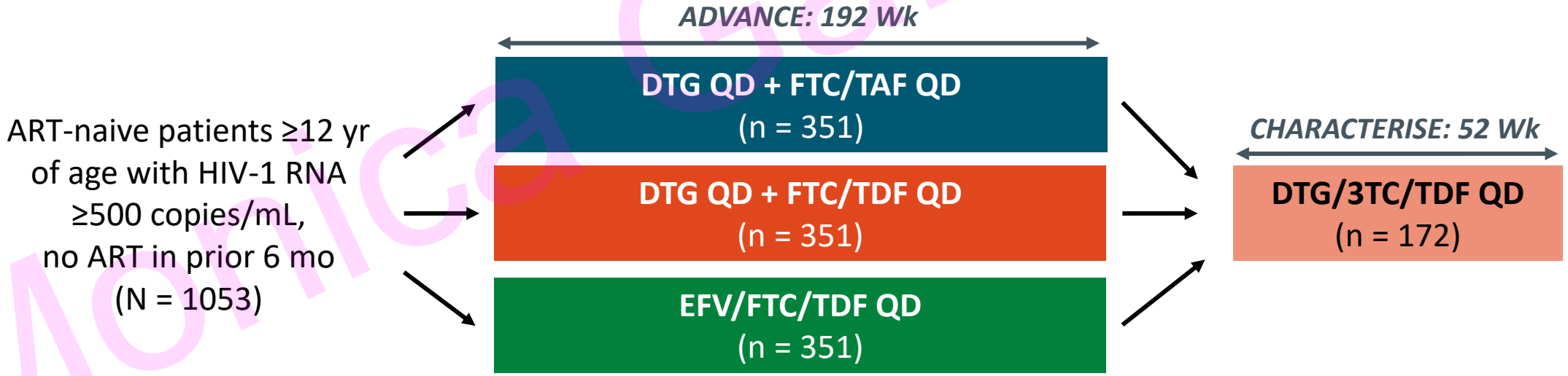


Estimated Weight Δ by Time From TDF to TAF Switch, kg/yr (95% CI)	INSTI (n = 3281)	NNRTI (n = 1452)	Boosted PI (n = 746)
-60 to 0 mos	0.42 (0.26 to 0.59)	0.66 (0.51 to 0.81)	0.31 (-0.02 to 0.64)
0 to 9 mos	2.64 (2.26 to 3.01)	2.25 (1.78 to 2.71)	1.98 (1.13 to 2.83)
9+ mos	0.29 (0.08 to 0.51)	0.20 (-0.14 to 0.54)	-0.11 (-0.57 to -0.35)

Mallon. AIDS 2020. Abstr OAB0604. Mallon JIAS 2021

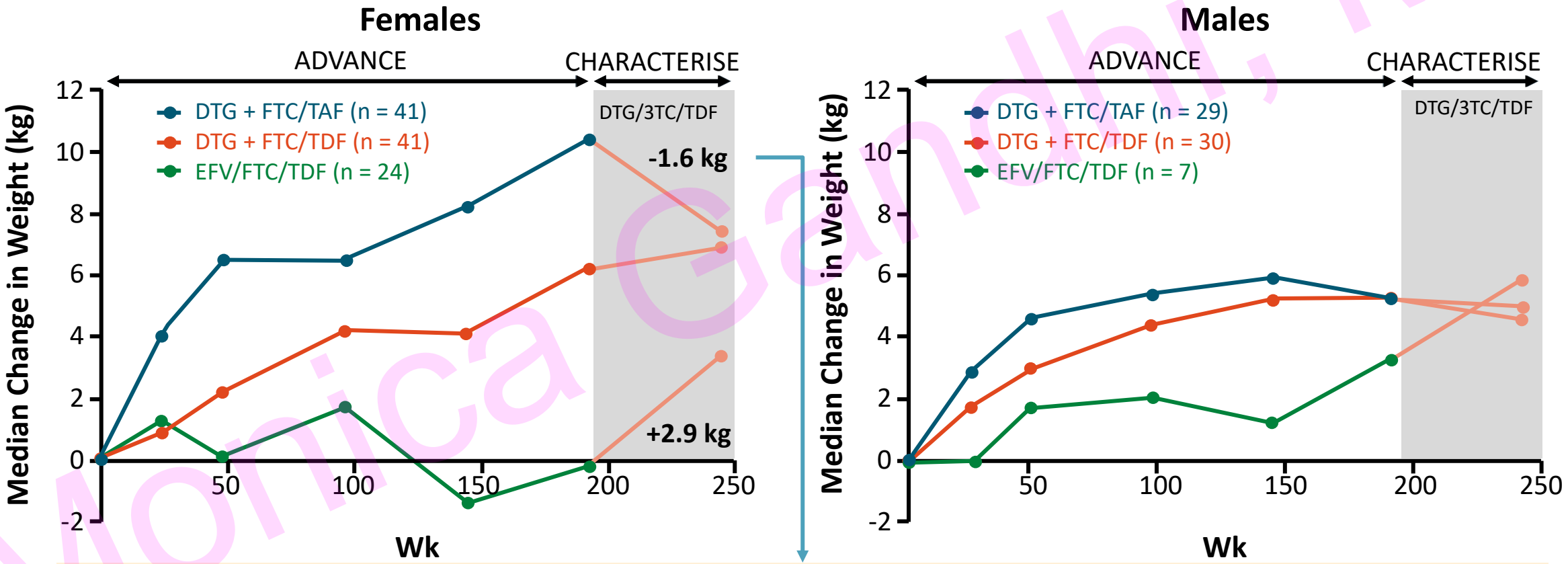
CHARACTERISE: Switch to DTG/3TC/TDF after ADVANCE trial participation

- **ADVANCE:** randomized, open-label phase III noninferiority trial in South Africa
  - HIV-1 RNA <50 copies/mL similar across treatment groups at Wk 48 (primary endpoint)[1] and through Wk 192,[2] but weight increases higher with DTG regimens: **+8.9 kg with DTG + FTC/TAF**, **+5.8 kg with DTG + FTC/TDF**, and **+3.3 kg with EFV/FTC/TDF** at Wk 192[2]
- **CHARACTERISE:** evaluation of weight and laboratory changes ≥52 wk after switch from ADVANCE trial to open-label DTG/3TC/TDF[3,4]



1. Venter. NEJM. 2019;381:803. 2. Venter. AIDS 2022. Abstr PELBB01. 3. **Bosch. CROI 2023. Abstr 167. 4**. Bosch. Clin Infect Dis. 2022;ciac949.

CHARACTERISE: Weight Change by Sex After Switch From ADVANCE Trial Regimens to DTG/3TC/TDF



In females, switch from **DTG + FTC/TAF** to **DTG/3TC/TDF** associated with median **1.6 kg weight loss**

Bosch. CROI 2023. Abstr 167.

CROI 2023 insights

- ***EFV to DTG:*** Efavirenz seems to be "anorectic" so starting DTG after EFV (IeDEA cohort) associated with more weight gain than after NVP
- **TAF to TDF**: Switching from TAF to TDF associated with more weight loss (both with DTG) in S. Africa women
- **DTG/3TC**: Small single site (Amsterdam) study but improved cholesterol & lean trunk mass to drop TAF

Themed Discussion-11 WEIGHT GAIN: DOES WHAT GOES UP ALWAYS COME DOWN?
Ballroom 1 (Level 5) **1:30 PM - 2:30 PM**

• Wednesday

671 *1:35*
WEIGHT LOSS AND METABOLIC CHANGES AFTER SWITCHING FROM TAF/FTC/DTG TO TDF/3TC/DTG
Bronwyn E. Bosch, Godspower Akpomiemie, Nomathemba Chandiwana, Simiso Sokhela, Andrew Hill, Kaitlyn McCann, Ambar Qavi, Manya Mirchandani, Francois Venter

672 *1:40*
FAVORABLE METABOLIC OUTCOMES 48 WEEKS AFTER SWITCH TO DTG/3TC
Sophie Degroote, Sophie Vanherrewege, Els Tobback, Els Caluwe, Lara Vincke, Wim Trypsteen, Mareva Delporte, Evy Blomme, Linos Vandekerckhove, Marie-Angélique De Scheerder
Research Group: the ATHENA national observational cohort

674 *1:45*
WEIGHT GAIN AMONG PARTICIPANTS SWITCHING TO A DOLUTEGRAVIR-BASED HIV REGIMEN IN KENYA
Kassem Bourgi, Susan Ofner, Beverly Musick, Kara Wools-Kaloustian, Lameck Diero, Constantin Yiannoutsos, Samir Gupta

CROI 2023, Seattle, February 2022

Clinical Infectious Diseases

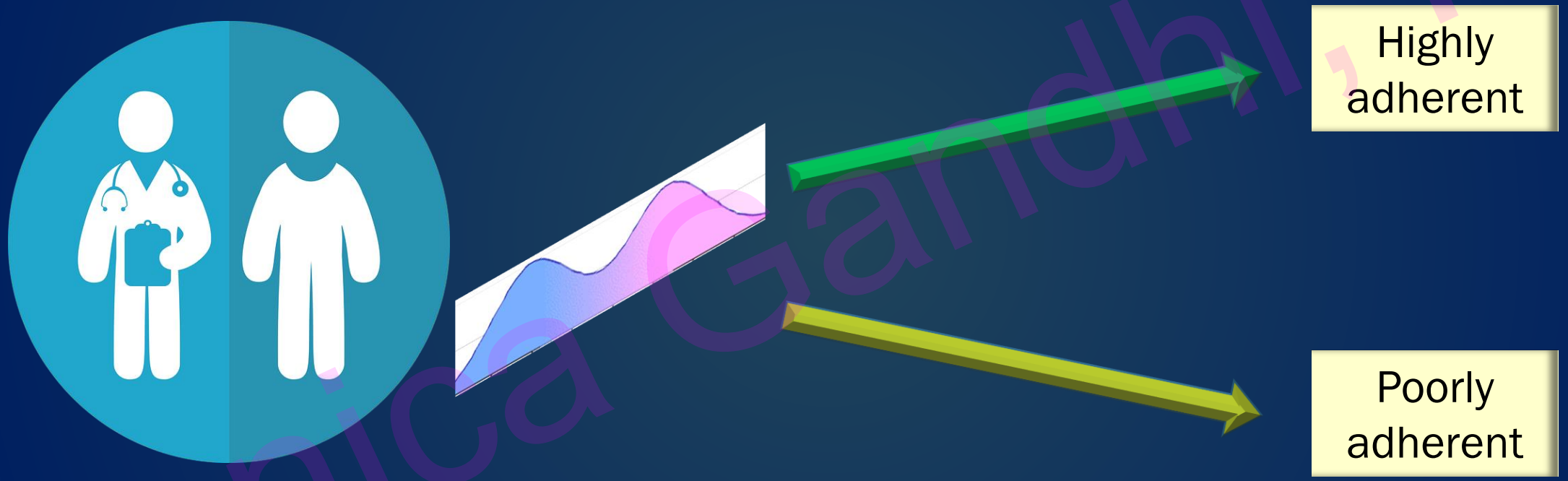
BRIEF REPORT

Weight and Metabolic Changes After Switching From Tenofovir Alafenamide (TAF)/Emtricitabine (FTC) +Dolutegravir (DTG), Tenofovir Disoproxil Fumarate (TDF)/FTC + DTG, and TDF/FTC/Efavirenz (EFV) to TDF/Lamivudine (3TC)/DTG

Bosch B. et al. CID April 2023; 76:8: 1492-5

Bottom line: TAF associated with more weight gain than TDF and Efavirenz suppresses weight

Patient with challenges to ART adherence could benefit from long-acting ART



Would then KNOW date of “medication consumption” (not adherence, but coming in), pharmacies or mobile vans administering the shots, home health

Original registrational trials of LA CAB/RPV- FLAIR, ATLAS and ATLAS 2M

FLAIR

- CAB/RPV LA in treatment naïve participants (K103N mutation allowed); First put on DTG/ABC/3TC for 20 weeks then LA ART with virologic suppression; 80% VS at 124 weeks

ATLAS

- CAB/RPV LA in treatment experienced participants every 4 weeks (K103N okay); on suppressive regimen for 6 months prior to switch; 97% VS rate 6 months

ATLAS 2M

- CAB/RPV LA in treatment experienced participants every 8 weeks (higher dose 600mg/900mg) after VS x ≥ 6 months; 97% VS at 152 weeks

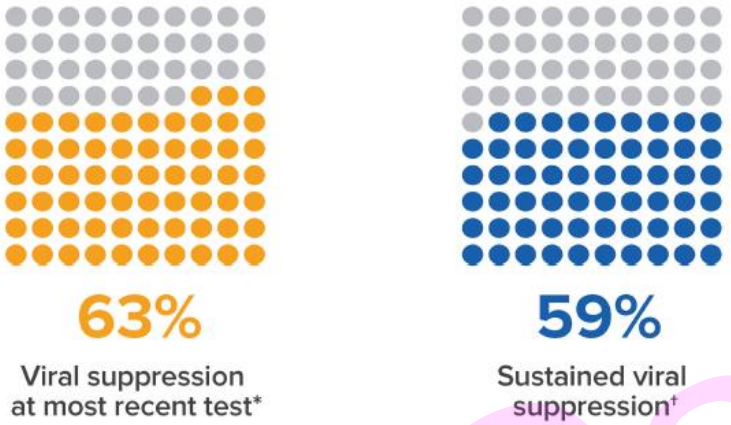
SOLAR (not registrational; after approval)

- CAB/RPV LA in treatment experienced participants every 8 weeks switched from BIC/TAF/FTC high rates of VS; 47% reported stigma (self or other) for LA ART

Orkin C. Lancet HIV 2021; Swindells S. AIDS 2022; Overton E. CID 2023; Ramgopal M. Lancet HIV 2023

Adherence Challenges with ARTs

Figure 4. Percentage of adults with diagnosed HIV who were virally suppressed during the 12 months befo… interview—Medical Monitoring Project, United States, 2020



Overall rates of VS in US 59% sustained (CDC HIV Special Surveillance Report 8/23)

Rates of virologic suppression worldwide:

- **In adults on ART, 79% suppression at 1 year, 65% by 3 years**
- In children/adolescents on ART, 36% suppression at 1 year, 24% at 3 years (Han. Lancet HIV 2021)

Barriers to ART adherence:

- Systematic review of 125 studies identified main barriers to ART adherence
- Forgetting
- Being away from home
- Change to daily routine
- Depression
- Alcohol/substance misuse
- Secrecy/stigma
- Feeling sick
- Far distance to clinic
- Stock outs

McComsey, G. A., et al. Real-World Adherence to Antiretroviral Therapy Among HIV-1 Patients Across the United States. *Advances in therapy*, *2021*
Min Han W et al. Global estimates of viral suppression in children and adolescents and adults on antiretroviral therapy adjusted for missing viral load measurements: a multiregional, retrospective cohort study in 31 countries. Lancet HIV 2021.
Shubber, Z., et al. Patient-Reported Barriers to Adherence to Antiretroviral Therapy: A Systematic Review and Meta-Analysis. *PLoS medicine, 2016.* 13(11), e1002183.
Altice, F., et al. . Adherence to HIV treatment regimens: systematic literature review and meta-analysis. *Patient preference and adherence*, 2019

METHODS

Inclusion criteria of trials:

- Virologically suppressed x at least 16 weeks on oral regimen first
- No history of virologic failure
- Only K103N in NNRTI; no INSTI mutations
- Oral CAB/RPV x 28 days but direct-to-inject approved FDA March ‘22

Inclusion criteria of Ward 86

- Need not be virologically suppressed or take oral ART before injectables
- No RPV or INSTI mutations (strengthened criteria later)
- **Express willingness to come to clinic q4 weeks, contact information, outreach from staff**
- Rigorous protocol, biweekly review of patients

Descriptive statistics summarized patient characteristics, median/range number of injections received, viral suppression outcomes, stratified by viral load ≥30 copies/mL at LA-ART initiation; Kaplan Meier plot for viremic

Implementation of program

- Hired pharm tech to help get injectable meds
- Biweekly meetings with Pharm D, pharm tech, clinic leadership, POP-UP program leadership to review each patient on injectables or being considered
- Protocol development with ongoing refinements based on observations in our pilot program
- 194 patients have been started on long-acting ART: rigorous protocol – will present first 133 here

Results

Table 1: Demographics and clinical characteristics of cohort in Ward 86 LA ART program (n=133)

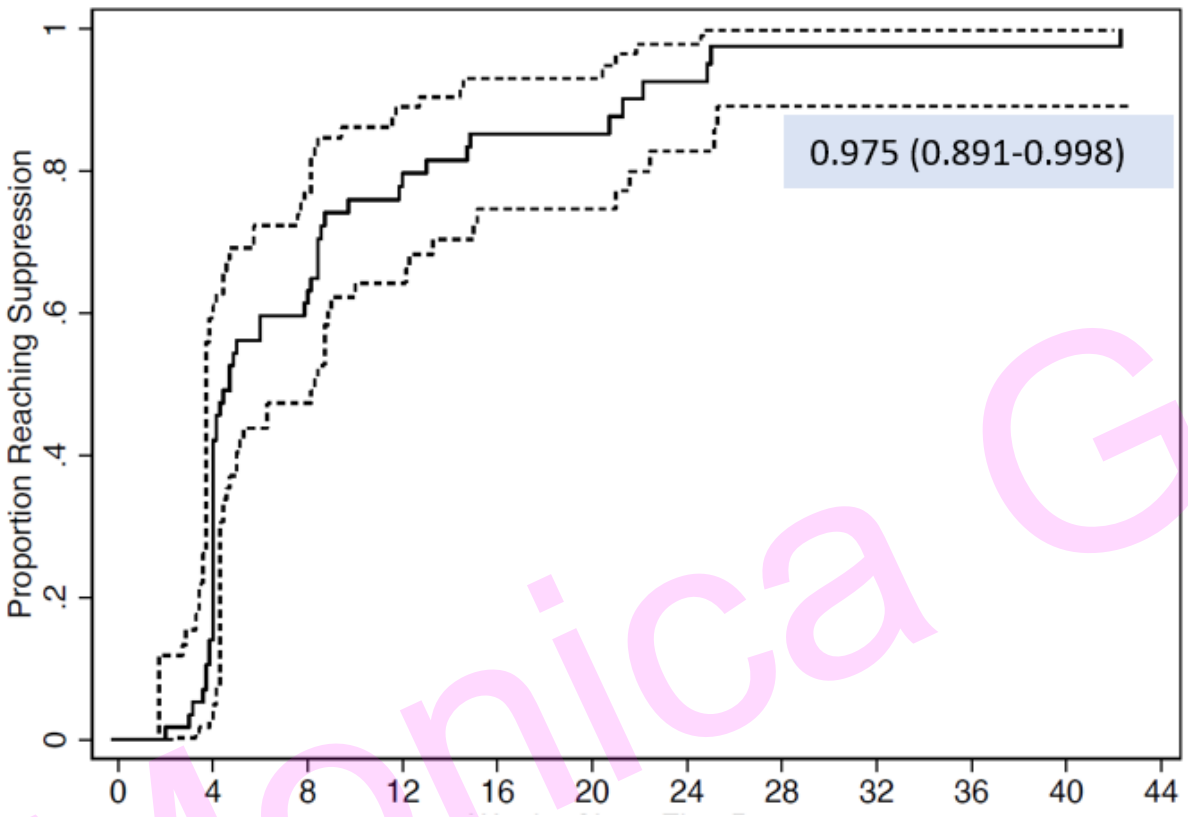
Characteristic	Distribution, n (%)	
Age (median, range)	45 (38-45) years	
Gender		
Cis Man	117 (88%)	
Cis Woman	11 (8%)	
Transgender Woman	5 (4%)	
Race/ethnicity		
Black	21 (16%)	
Latino/a	50 (38%)	
White	43 (32%)	
Multiracial	19 (14%)	
Housing		
Unstable	77 (58%)	
Stable	45 (34%)	
Homeless	11 (8%)	
Insurance		
Medicare or Medicaid or both	130 (98%)	
ADAP	3 (2%)	
Current stimulant use	44 (33%)	
Major mental illness	51 (38%)	
Virologically non-suppressed (>30 copies/ml)	57 (43%) with log10 viral load (mean, STD) 4.21 (1.30)	
CD4 count (median with interquartile range)	Virologically suppressed	616 (395–818)
	Virologically non-suppressed	215 (75–402)

* Note: ADAP is AIDS Drug Assistance Program; Baseline CD4 defined as the CD4 count closest to and including date of first injection. Median time from CD4 count to first injection was 70 (range 0 to 882) days

- Between June 2021-November 2022, 133 PWH started on LA-ART, 76 suppressed on oral ART, 57 (43%) with viremia
- Diverse (68% non-White; 88 (66%) unstably housed; 44 (33%) endorsed substance use)
- Median CD4 count in those with viremia lower than those w/ suppression
- 74% (66-81%) on-time injections
- In those with virologic suppression, 100% (95% CI 94%-100%) remained suppressed (median 26 weeks (2-42) for whole cohort)

Results (continued)

Figure: KM curve of probability of reaching virologic suppression (VL <30) on LA ART (n=57); dotted lines 95% CI



Neither patient who didn't have virologic suppression could take oral ART

- Among viremic PWH, at median of 33 days, 55 suppressed, 2 had early virologic failure.
- 97.5% (89.1 to 99.9%) expected to achieve virologic suppression by median 26 weeks
- Current cohort virologic failure rate 1.5% similar to that across clinical trials (1.4%) by 48 weeks (68% by 24 weeks)
- Two failures < 24 weeks, both had minor mutations so protocol tightened; 3rd didn't suppress <100 (182) so added LEN

Virologic failure #1: Started with V179I mutations, didn't show 2 $\log_{10}$ reduction by 1st visit (baseline viral load 214,540 → 39,293 copies/mL); Developed Y181C, L100I

Virologic failure #2: Started with T97A mutation, didn't show 2 $\log_{10}$ reduction by 1st (baseline viral load 137,134 → 4,371 copies/mL); Developed R263K, E138K mutations

Case

57 yo man with HIV dx'd 1998, CD4 nadir <50, thrush in past

ART history

- AZT monotherapy x 6 months then dual NRTI therapy
- In mid '90's, ddI/d4T/indinavir/ritonavir as well as nelfinavir and saquinavir/RTV
- In 2001, TDF/FTC/EFV for many years with drug holidays but then viremia, NNRTI mutations
- Switched to ATV/r + RAL + TDF/FTC and eventually DRV/cobi + DTG + TAF/FTC. Suppressed but pill fatigue precludes ongoing use

Cumulative mutation history on genotypes:

- NRTI: K67N, K219Q, T215I, M184V,
- PI: M46L
- NNRTI: G190S, V106I, F227L, V179T
- INSTI: none
- Not CCR5 tropic (10/2019)

71

Case (continued)

- Despite adherence counseling, viral load now >1.5 million, CD4 142 cells/mm^3
- Patient cannot take oral ART anymore
- Started patient on lenacapavir 600mg (300mg oral dose x 2) on day 0 and 1 with lenacapavir 927mg sq on day 0
- Added cabotegravir 600mg IM that day and 450mg every month
- Viral load dropped 2-log HIV RNA within 1 week and undetectable by 2 months after starting this regimen

- **Bottom line**: STUDY PROPOSED IN THE ACTG OF LONG-ACTING LEN + LONG-ACTING CABOTEGRAVIR IN PARTICIPANTS WITH NNRTI RESISTANCE (~10% WORLDWIDE- WHO resistance report Nov '21)

BIGGEST UPDATES IN PREVENTION, CURE, VACCINES 2023

AETC AIDS Education & Training Center Program Midwest

Biggest update in HIV prevention in 2022

Cisgender women→ Daily TDF/FTC or IM cabotegravir

MSM, transgender women, other populations → Daily TDF/FTC or daily TAF/FTC or 2:1:1 TDF/FTC (intermittent) IM cabotegravir

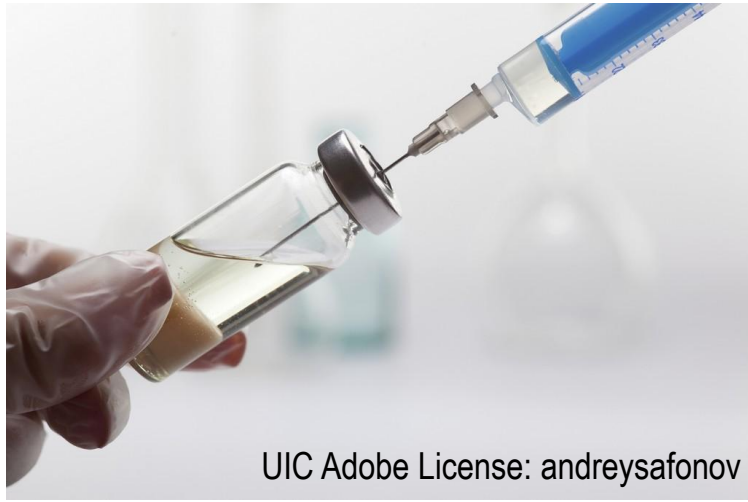
FDA Approves First Injectable Treatment for HIV Pre-Exposure Prevention

Drug Given Every Two Months Rather Than Daily Pill is Important Tool in Effort to End the HIV Epidemic

Share | Tweet | Linkedin | Email | Print

ss Announcements

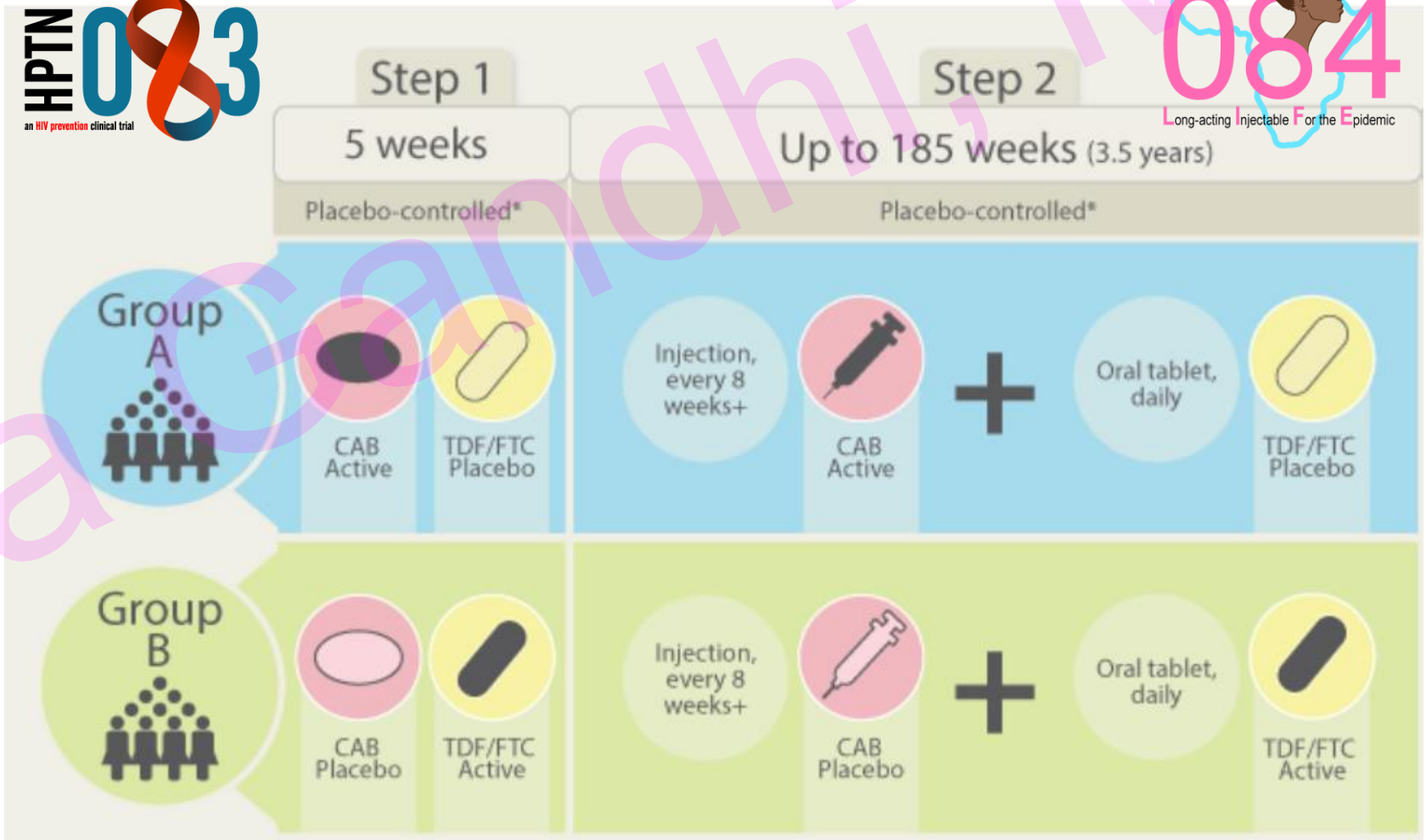
For Immediate Release: December 20, 2021



UIC Adobe License: andreysafonov

HPTN 083 and 084 studies
Long-acting PrEP with cabotegravir

- Phase 2b/3 randomized, double-blind, double-dummy studies
  - ➢Oral lead in phase with PO (placebo v CAB) 5 weeks
  - ➢Transition to Q8w injections (placebo v CAB)
  - ➢Both showed superiority of CAB over TDF/FTC for prevention (66% MSM/TGW; 89% cis-gender women)



HPTN press release

World Health Organization

WHO recommends long-acting cabotegravir for HIV prevention

New WHO guidelines advise countries to deliver long-acting cabotegravir as part of comprehensive approach to HIV prevention

28 July 2022 | News release | Reading time: 3 min (830 words)

Summary of resistance mutations across HPTN083, including open label (CAB alone, look at bolded mutations)

The table shows all INSTI resistance associated mutations (RAMs) detected in cases in the cabotegravir arm of HPTN 083. The mutations shown were detected at one or more study visits. Major INSTI RAMs are bolded.

ID Code	HIV Subtype	INSTI RAMs detected
A2	C	M50I, **E138K, Q148K**
A3	B	T97A
B3	AE	V151I
B6	B	M50I
B8	B	L74I
B9	B	L74I
B11	B	L74I
B15	B	M50M/I
C1	B	L74I, Q146Q/R, **E138E/K**, **G140G/S**, **Q148R**, E157Q
C3	B	**E138A**, **Q148R**
D1	Likely B	Q146L, **Q148R**, **N155H, R263K**
D2	Likely B	**N155H**, S230R
D3	BF	**R263K**
D4	C	M50I, **E138K**, **G140A**, **Q148R**
D5	F	M50I, **R263K**
D6	AE	L74I, **Q148R**
DX2	BF	V151I
BR1	BC	**Q148R**

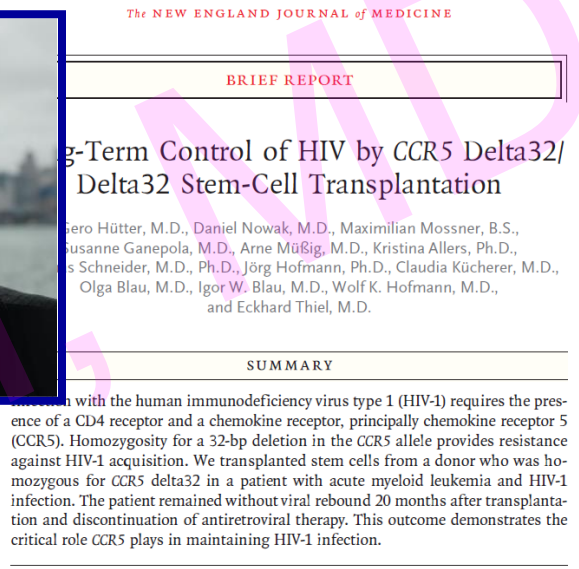
Yes, N155H came out in CAB breakthroughs in treatment and prevention trials

Markzinke M et al. Extended Analysis of HIV Infection in Cisgender Men and Transgender Women Who Have Sex with Men Receiving Injectable Cabotegravir for HIV Prevention: HPTN 083. AAC April 2023

HIV Cure

In Medical Breakthrough, A Sixth Person May Have Been Cured of HIV

July 21, 2023



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

g-Term Control of HIV by *CCR5* Delta32/Delta32 Stem-Cell Transplantation

ero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S., usanne Ganepola, M.D., Arne Müßig, M.D., Kristina Allers, Ph.D., s Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D., Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D., and Eckhard Thiel, M.D.

SUMMARY

n with the human immunodeficiency virus type 1 (HIV-1) requires the presence of a CD4 receptor and a chemokine receptor, principally chemokine receptor 5 (CCR5). Homozygosity for a 32-bp deletion in the *CCR5* allele provides resistance against HIV-1 acquisition. We transplanted stem cells from a donor who was homozygous for *CCR5* delta32 in a patient with acute myeloid leukemia and HIV-1 infection. The patient remained without viral rebound 20 months after transplantation and discontinuation of antiretroviral therapy. This outcome demonstrates the critical role *CCR5* plays in maintaining HIV-1 infection.

- Cure may be too powerful & promising a term
  - Remission probably better
- Two types: both after finite duration of therapy
  - Eradication/Sterilizing: no replication-competent proviruses left
  - Functional/Non-Sterilizing: control of viral replication w/o ART

Slide courtesy of John Mellors MD

HIV mRNA vaccines for HIV & cure!

Phase 3 Mosaico HIV vaccine efficacy trial stopped early due to lack of benefit

Monday, March 14, 2022

NIH launches clinical trial of three mRNA HIV vaccines

Phase 1 study is among first to examine mRNA technology for HIV.

nature medicine

Article | Published: 09 December 2021

A multiclade *env–gag* VLP mRNA vaccine elicits tier-2 HIV-1-neutralizing antibodies and reduces the risk of heterologous SHIV infection in macaques

Peng Zhang, Elisabeth Narayanan, ... Paolo Lusso + Show authors

Nature Medicine **27**, 2234–2245 (2021) | Cite this article

stop aids. make the promise

Thank you to Renslow Sherer MD, Diane Havlir MD, Division of HIV, ID and Global Medicine, the HIV movement, and Ward 86!

MATEC Resources

- National Clinician Consultation Center
  http://nccc.ucsf.edu/
  - HIV Management
  - Perinatal HIV
  - HIV PrEP
  - HIV PEP line
  - HCV Management
  - Substance Use Management
- AETC National HIV Curriculum
  https://aidsetc.org/nhc
- AETC National HIV-HCV Curriculum
  https://aidsetc.org/hivhcv
- Hepatitis C Online
  https://www.hepatitisc.uw.edu
- AETC National Coordinating Resource Center
  https://aidsetc.org/
- Additional Trainings https://matec.info

AETC AIDS Education & Training Center Program Midwest