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

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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
What type of virus is HIV?

- HIV – “lentivirus”, subgroup of retroviruses
  - Lentivirus 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?

1) Chimpanzees, Gorillas
2) Monkeys; Mandrills
3) African Green Monkeys, Baboons
4) Sooty Mangabeys
5) Sykes’ Monkeys

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

HIV-1

- Pandemic strain (90% of world infections)
- Many clades
  - Group M
  - Group N
  - Group O
  - Group P

HIV-1 subtypes:
- 7 subtypes (A-G)

HIV-2

- SIV from sooty mangabeys

SIV from chimpanzees

SIV from gorillas
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

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

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
Global HIV prevalence in adults, 1995

Adult prevalence rate
- 15.0 - 34.0%
- 5.0 - <15.0%
- 1.0 - <5.0%
- 0.5 - <1.0%
- 0.1 - <0.5%
- <0.1%

MONICA GANDHI, MD
Global HIV prevalence in adults, 2005

Monica Gandhi, MD
Adults and children estimated to have HIV 2022

North America and western and central Europe
Total: 39.0 million
2.3 million
[1.9 million–2.6 million]

Middle East and North Africa
190,000
[160,000–220,000]

Western and central Africa
4.8 million
[4.2 million–5.5 million]

Eastern Europe and central Asia
2.0 million
[1.8 million–2.1 million]

Asia and the Pacific
6.5 million
[5.3 million–7.8 million]

Eastern and southern Africa
20.8 million
[17.4 million–24.5 million]

Latin America
2.2 million
[2.0 million–2.5 million]

Caribbean
330,000
[290,000–380,000]

North America and western and central Europe

Total: 39.0 million
[33.1 million–45.7 million]

Monica Gandhi, MD
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

<table>
<thead>
<tr>
<th>Category</th>
<th>Estimate</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>People with HIV</td>
<td>39.0 million</td>
<td>[33.1 million–45.7 million]</td>
</tr>
<tr>
<td>New HIV infections</td>
<td>1.3 million</td>
<td>[1.0 million–1.7 million]</td>
</tr>
<tr>
<td>Deaths due to AIDS</td>
<td>630 000</td>
<td>[480 000–880 000]</td>
</tr>
</tbody>
</table>
Figure 12.1 Number of new HIV infections, global, 1990–2022, and 2025 target

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.
HIV in the United States
First clinical descriptions of AIDS, 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.

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
Contrary to what you've heard, AIDS isn't a threat to the vast majority of heterosexuals or a peril to humanity. It is—and is likely to remain—largely the fatal price one can pay for anal intercourse.
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 Art 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 p.m. 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 1579, San Francisco, CA 94111
Phone: 415-788-2433

AND SEQUINS... LOTS OF SEQUINS.
October 1987, Washington Mall
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”


2003 – PEPFAR program formed

2010 – National HIV/AIDS Strategy

2019 – End the HIV Epidemic initiative

Monica Gandhi, MD
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 10 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

Total = 66.8%

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

1983- Present

Investigational Trials

Women's Clinic
Universal ART
RAPID start
PrEP
SALUD Clinic-Latino/a
Golden Compass-HIV & aging
POP-UI Homeless Clinic
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)
**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

- HIV treatment and prevention care
- Primary and preventative medical care
- Mental health care
- Substance use care
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)

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BICTEGRAVIR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1489</td>
<td>Naïve</td>
<td>DTG/ABC/3TC</td>
<td>Non-inferior</td>
<td>0</td>
</tr>
<tr>
<td>1490</td>
<td>Naïve</td>
<td>DTG+FTC/TAF</td>
<td>Non-inferior</td>
<td>0</td>
</tr>
<tr>
<td>1844</td>
<td>Suppressed</td>
<td>DTG/ABC/3TC</td>
<td>Non-inferior</td>
<td>0</td>
</tr>
<tr>
<td>1878</td>
<td>Suppressed</td>
<td>Boosted PI + 2 NRTIs</td>
<td>Non-inferior</td>
<td>0 to INSTI but 1 L74V in PI arm</td>
</tr>
<tr>
<td>1961</td>
<td>Suppressed</td>
<td>E/C/F/(TAF or TDF) ATV+RTV + FTC/TDF</td>
<td>Non-inferior</td>
<td>0 to INSTI but 1 M184V in ELV/cobi</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DOLUTEGRAVIR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SINGLE</td>
<td>Naïve</td>
<td>EFV/TDF/FTC</td>
<td>Superior</td>
<td>0 in DTG arm; 7 in EFV</td>
</tr>
<tr>
<td>FLAMINGO</td>
<td>Naïve</td>
<td>DRV/r with 2 NRTI backbone</td>
<td>Superior</td>
<td>0 in either</td>
</tr>
<tr>
<td>SPRING-2</td>
<td>Naïve</td>
<td>RAL with 2 NRTI backbone</td>
<td>Non-inferior</td>
<td>0 in DTG; 1 INSTI/NRTI in RAL</td>
</tr>
</tbody>
</table>
Accumulating data for INSTIS as 2\textsuperscript{ND} 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

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

**Table 2. Comparison of DTG 50 mg twice daily versus PCB-I 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**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>DTG 50 mg twice daily change from BL at day 8 (n=14)</th>
<th>PCB-I 50 mg twice daily change from BL at day 8 (n=16)</th>
<th>Combined arms, HIV-1 RNA &lt;50 copies/mL (%)) (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>14*</td>
<td>1.06 (0.17)</td>
<td>16</td>
</tr>
<tr>
<td>DTG FC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2.5</td>
<td>4</td>
<td>-1.13 (0.82)</td>
<td>7</td>
</tr>
<tr>
<td>&gt;2.5–4</td>
<td>2</td>
<td>-1.22 (0.65)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;4–9</td>
<td>5</td>
<td>-0.99 (0.63)</td>
<td>4</td>
</tr>
<tr>
<td>&gt;10–20</td>
<td>1</td>
<td>-0.96</td>
<td>1</td>
</tr>
<tr>
<td>&gt;20</td>
<td>1</td>
<td>-0.16</td>
<td>1</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>-1.32</td>
<td>0</td>
</tr>
<tr>
<td>Derived IN mutation group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Q148*</td>
<td>5</td>
<td>-1.43 (0.745)</td>
<td>9</td>
</tr>
<tr>
<td>Q148 +1’</td>
<td>6</td>
<td>-0.87 (0.587)</td>
<td>6</td>
</tr>
<tr>
<td>Q148 +≥2’</td>
<td>3</td>
<td>-0.90 (0.758)</td>
<td>1</td>
</tr>
<tr>
<td>OSS* of background ART</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Bisher A. Antivir Ther. 2015;20(3):343-8
## Recent studies of DTG with NRTI resistance

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

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

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

Patients (%) with HIV-1 RNA <50 copies/mL at Week 24

Number of Darunavir mutations at baseline

- 2 mutations: 50%
- 3 mutations: 22%
- ≥4 mutations: 10%


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
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.

- **Placebo plus OBT**
- **Maraviroc once daily plus OBT**
- **Maraviroc twice daily plus OBT**

**HIV-1 RNA Suppression**

- <400 copies/mL
- <50 copies/mL

**Must assess CCR5 tropism prior to using this medication**

Adding maraviroc to OBT was associated with improved viral suppression.

**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).

**Randomized Cohort**
- HTE adults failing current; have 1-2 remaining ARV classes (≥ 1 fully active available agent/ class), unable to construct viable regimen with remaining agents (n = 272)

**Nonrandomized Cohort**
- HTE adults failing current ART with 0 remaining ARV classes and no fully active agents (n = 99)

### Blinded Phase
- **FTR 600 mg BID + Failing Regimen (n = 203)**
- **Placebo BID + Failing Regimen (n = 69)**

### Primary Endpoint
- Adjusted* Mean Δ in HIV-1 RNA at Day 8 vs Day 1 Day 9 log₁₀ c/mL (95% CI)
  - **FTR 600 mg BID + OBT†**
    - Δ = -0.79 (-0.88 to -0.70)
  - **FTR 600 mg BID + OBT†**
    - Δ = -0.17 (-0.33 to -0.01)

### Open-Label Extension
- **FTR 600 mg BID + OBT†**

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

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

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)

**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

**RESEARCH ARTICLE**

Weight gain among treatment-naive 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 R. Rebeiro,1 Bryan E. Shepherd,1 Frank Palella,1 Richard D. Moore,1 Karl M. Kibbe,1 John C. Hughes,1 Arvind Arun,1,2 Marni C. cooper,3 Richard D. Moore,1,3

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

- 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

* Differences between arms not statistically significant.

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

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).

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)

<table>
<thead>
<tr>
<th>Time</th>
<th>INSTI (n = 3281)</th>
<th>NNRTI (n = 1452)</th>
<th>Boosted PI (n = 746)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-60 to 0 mos</td>
<td>0.42 (0.26 to 0.59)</td>
<td>0.66 (0.51 to 0.81)</td>
<td>0.31 (-0.02 to 0.64)</td>
</tr>
<tr>
<td>0 to 9 mos</td>
<td>2.64 (2.26 to 3.01)</td>
<td>2.25 (1.78 to 2.71)</td>
<td>1.98 (1.13 to 2.83)</td>
</tr>
<tr>
<td>9+ mos</td>
<td>0.29 (0.08 to 0.51)</td>
<td>0.20 (-0.14 to 0.54)</td>
<td>-0.11 (-0.57 to -0.35)</td>
</tr>
</tbody>
</table>
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\(^3,4\)

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

Monica Gandhi, MD

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

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

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

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

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)

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

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

* 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

Gandhi Annals of Internal Medicine 2023
Results (continued)

- 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 1\(^{st}\) 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 1\(^{st}\) (baseline viral load 137,134 → 4,371 copies/mL); Developed R263K, E138K mutations.

**Neither patient who didn’t have virologic suppression could take oral ART**
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)
Case (continued)

- Despite adherence counseling, viral load now >1.5 million, CD4 142 cells/mm³
- 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
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

For Immediate Release: December 20, 2021
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
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.

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

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

- 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  

*Nature Medicine* 27, 2234–2245 (2021) | Cite this article
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/](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](https://aidsetc.org/nhc)

- AETC National HIV-HCV Curriculum
  [https://aidsetc.org/hivhcv](https://aidsetc.org/hivhcv)

- Hepatitis C Online
  [https://www.hepatitisc.uw.edu](https://www.hepatitisc.uw.edu)

- AETC National Coordinating Resource Center
  [https://aidsetc.org/](https://aidsetc.org/)

- Additional Trainings
  [https://matec.info](https://matec.info)