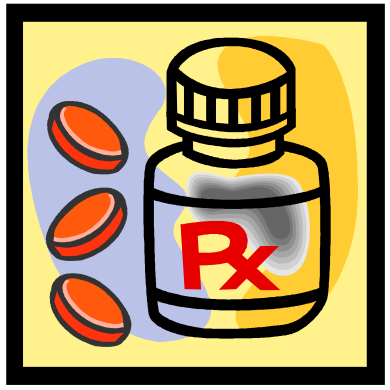
Antiretroviral Therapy for the Management of HIV
Past, Present, and Future

March 14, 2024



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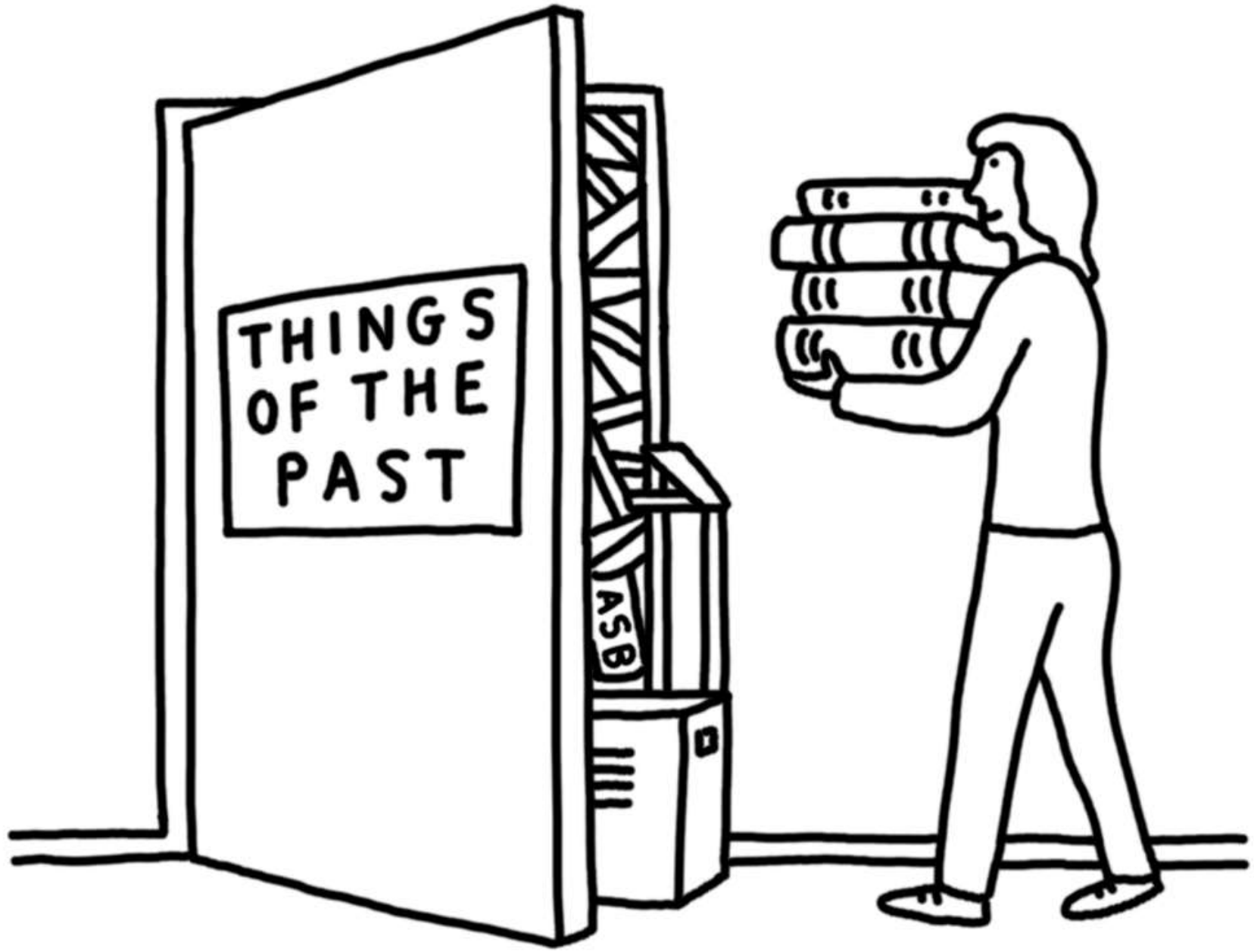
Objectives

- Upon completion of this session, learners should be able to:
  - Review historical data on HIV therapeutics
  - Select a HIV regimen for a patient newly diagnosed with HIV
  - Identify new compounds in development for treatment of HIV


THINGS
OF THE
PAST
ASB

CENTERS FOR DISEASE CONTROL

June 5, 1981 / Vol. 30 / No. 21

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

Epidemiologic Notes and Reports

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.

Patient 1: A previously healthy 33-year-old man developed *P. carinii* pneumonia and oral mucosal candidiasis in March 1981 after a 2-month history of fever associated with elevated liver enzymes, leukopenia, and CMV viruria. The serum complement-fixation CMV titer in October 1980 was 256; in May 1981 it was 32.* The patient's condition deteriorated despite courses of treatment with trimethoprim-sulfamethoxazole (TMP/SMX), pentamidine, and acyclovir. He died May 3, and postmortem examination showed residual *P. carinii* and CMV pneumonia, but no evidence of neoplasia.

Patient 2: A previously healthy 30-year-old man developed *P. carinii* pneumonia in April 1981 after a 5-month history of fever each day and of elevated liver-function tests, CMV viruria, and documented seroconversion to CMV, i.e., an acute-phase titer of 16 and a convalescent-phase titer of 28* in anticomplement immunofluorescence tests. Other features of his illness included leukopenia and mucosal candidiasis. His pneumonia responded to a course of intravenous TMP/SMX, but, as of the latest reports, he continues to have a fever each day.

Patient 3: A 30-year-old man was well until January 1981 when he developed esophageal and oral candidiasis that responded to Amphotericin B treatment. He was hospitalized in February 1981 for *P. carinii* pneumonia that responded to oral TMP/SMX. His esophageal candidiasis recurred after the pneumonia was diagnosed, and he was again given Amphotericin B. The CMV complement-fixation titer in March 1981 was 8. Material from an esophageal biopsy was positive for CMV.

Patient 4: A 29-year-old man developed *P. carinii* pneumonia in February 1981. He had had Hodgkins disease 3 years earlier, but had been successfully treated with radiation therapy alone. He did not improve after being given intravenous TMP/SMX and corticosteroids and died in March. Postmortem examination showed no evidence of Hodgkins disease, but *P. carinii* and CMV were found in lung tissue.

*Paired specimens not run in parallel.

CENTERS FOR DISEASE CONTROL

July 3, 1981 / Vol. 30 / No. 25

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

Epidemiologic Notes and Reports

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 shown in Table 1.

Skin or mucous membrane lesions, often dark blue to violaceous plaques or nodules, were present in most of the patients on their initial physician visit. However, these lesions were not always present and often were considered benign by the patient and his physician.

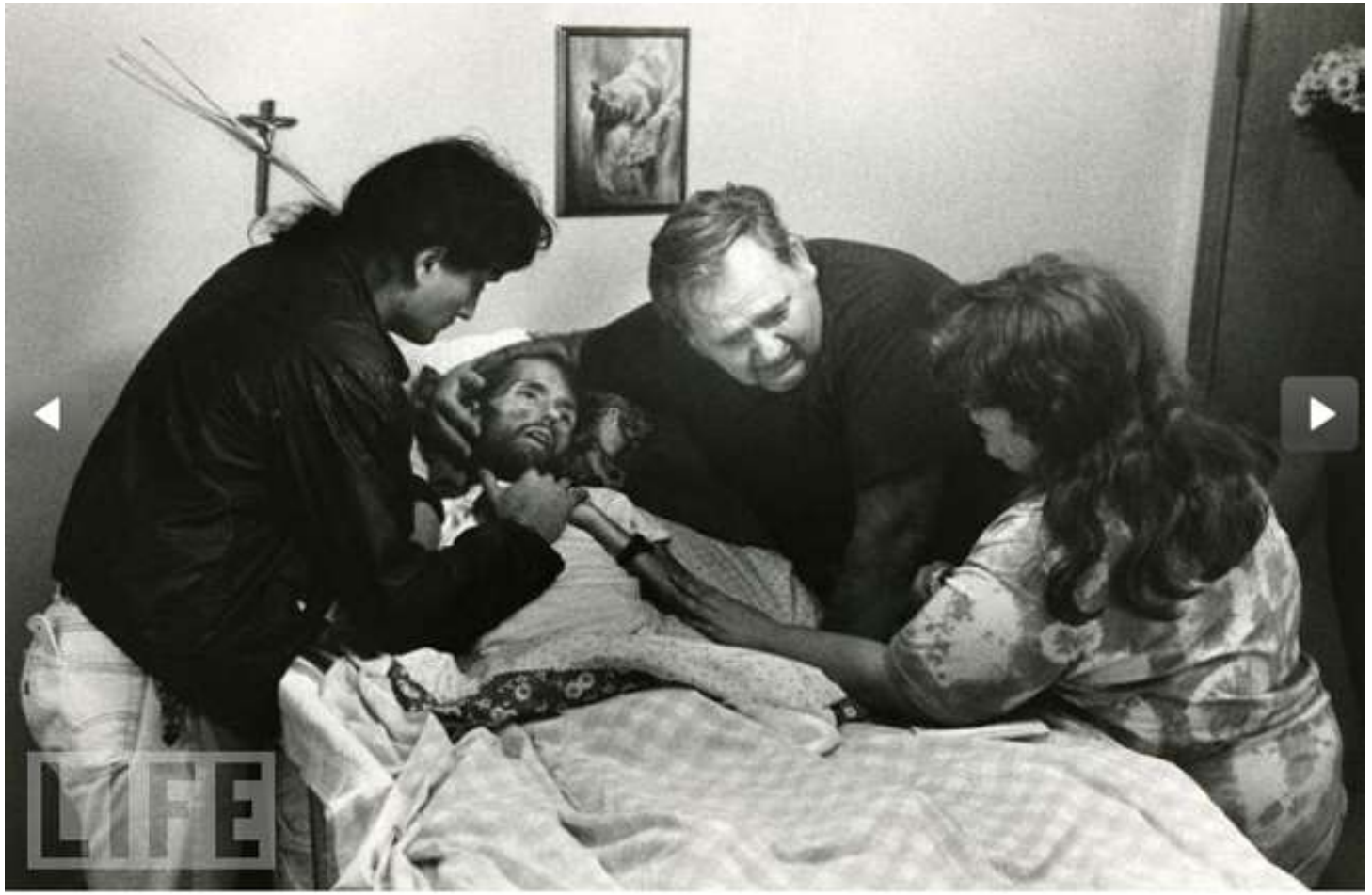
A review of the New York University Coordinated Cancer Registry for KS in men under age 50 revealed no cases from 1970-1979 at Bellevue Hospital and 3 cases in this age group at the New York University Hospital from 1961-1979.

Seven KS patients had serious infections diagnosed after their initial physician visit. Six patients had pneumonia (4 biopsy confirmed as due to *Pneumocystis carinii* [PC]), and one had necrotizing toxoplasmosis of the central nervous system. One of the patients with *Pneumocystis* pneumonia also experienced severe, recurrent, herpes simplex infection; extensive candidiasis; and cryptococcal meningitis. The results of tests for cytomegalovirus (CMV) infection were available for 12 patients. All 12 had serological evidence of past or present CMV infection. In 3 patients for whom culture results were available, CMV was isolated from blood, urine and/or lung of all 3. Past infections with amebiasis and hepatitis were commonly reported.

TABLE 1. Presenting complaints in 20 patients with Kaposi's sarcoma

Presenting complaint	Number (percentage) of patients
Skin lesion(s) only	10 (50%)
Skin lesions plus lymphadenopathy	4 (20%)
Oral mucosal lesion only	1 (5%)
Inguinal adenopathy plus perirectal abscess	1 (5%)
Weight loss and fever	2 (10%)
Weight loss, fever, and pneumonia (one due to *Pneumocystis carinii*)	2 (10%)

HIV in 1982



Median Survival was 8-15 months

The NEW ENGLAND
JOURNAL of MEDICINE

The New England
Journal of Medicine

Volume 317 JULY 23, 1987 Number 4

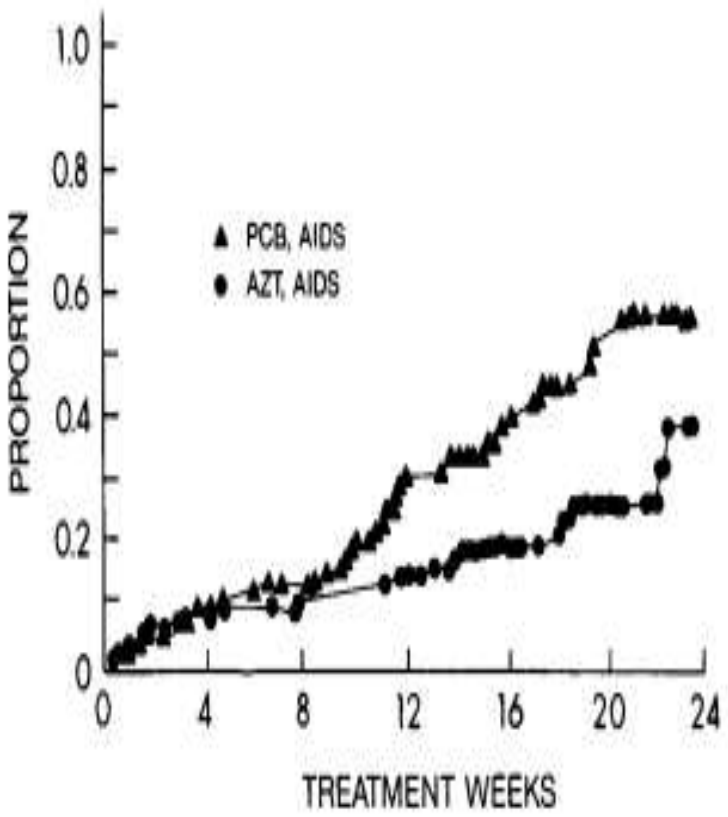
THE EFFICACY OF AZIDOTHYMIDINE (AZT) IN THE TREATMENT OF PATIENTS WITH AIDS AND AIDS-RELATED COMPLEX

A Double-Blind, Placebo-Controlled Trial

MARGARET A. FISCHL, M.D., DOUGLAS D. RICHMAN, M.D., MICHAEL H. GRIECO, M.D., J.D., MICHAEL S. GOTTLIEB, M.D., PAUL A. VOLBERDING, M.D., OSCAR L. LASKIN, M.D., JOHN M. LEEDOM, M.D., JEROME E. GROOPMAN, M.D., DONNA MILDVAN, M.D., ROBERT T. SCHOOLEY, M.D., GEORGE G. JACKSON, M.D., DAVID T. DURACK, M.B., D.PHIL., DANNIE KING, PH.D., AND THE AZT COLLABORATIVE WORKING GROUP

AZT (Zidovudine) vs placebo for treatment of advanced HIV disease

- Placebo-controlled, double-blind study
- Participants randomized to AZT 250 mg every 4 hours or placebo
- 282 enrolled, all but 13 men
- Study terminated early due to imbalance in deaths and HIV-related opportunistic infections
  - Nineteen in the placebo group and 1 in the AZT group dies during the study ($p < 0.001$)
- Treatment complicated by significant bone marrow suppression, including transfusion-requiring anemia



Era of optimism about AZT monotherapy was brief

says Amos. This is one reason why, in spite of the tremendous interest in using the technique, very little is yet in print. Terry Burke, of the University of Leicester, also points out that it is dangerous to assume that the band patterns produced by the technique is in fact a fingerprint, that most of the bands represent independently inherited loci.

"You have to demonstrate you have a true fingerprint with each new species you look at," says Burke, "and this involves a lot of work, with several crosses." So far, he notes, data demonstrating true fingerprints have been published only for human, dog, cat, mouse, and the house sparrow, although some unpublished data exist, including that for the European bee-eater.

In spite of these caveats, many researchers are pressing ahead, and results are beginning to come into the literature. For instance, Burke and his colleague M. W. Bruford have already demonstrated that about 20% of house sparrow chicks in the nests of apparently monogamous pairs are fathered by other males. The female is deceived on occasion too, when another female lays an egg in her nest, a trick known as intraspecific parasitism. In both cases, the reproductive success of the adults on the nest is lower than would have been calculated from field observations—unless they have been plying similar tricks elsewhere.

Davis, in collaboration with Burke, is soon to publish data on the hedge sparrow, whose mating system is very much more complicated. The results give a clearer insight into true reproductive success in this species and demonstrate that the birds' behavior is finely tuned to that parameter, even though the fit is not perfect.

These investigations rely on the ability of fingerprint data to identify parent-offspring relationships, which is not very controversial. In their work with the bee-eaters, Krebbs and his colleagues stray into uncertain territory, that of detecting more distant relationships. "In our population we have about a 20 to 30% sharing of bands by chance, which means that we are fairly confident of identifying full siblings," says Krebbs. For their purposes, this represents an acceptable level of background noise. "First cousins, with 12.5% genetic relationship, would be more difficult to detect, but we would not expect a significant degree of help at the nest with this distant a relationship."

The clash between high expectations and pedestrian reality is imminent in the joint DNA fingerprinting/behavioral ecology endeavor. Some problems will be solved readily, others will not, but overall it does represent major progress. ■ ROGER LEWIN

24 MARCH 1989

Drug-Resistant Strains of AIDS Virus Found

The emergence of AZT-resistant strains of the AIDS virus in patients treated with the drug has serious implications for treating AIDS and preventing its spread

THE BURROUGHS WELLCOME CO. announced last week that prolonged treatment with AZT, the only drug now approved for combating AIDS infections, can lead to the emergence of drug-resistant strains of the AIDS virus. The appearance of the AZT-resistant strains was not associated with any marked decline in the patients' conditions, and clinicians say that AIDS patients who are taking the drug do not need to change

The AIDS virus becomes progressively more resistant to AZT as time goes on.

their treatment regimens. The new findings, which will be published in the 31 March issue of *Science*, nonetheless have serious implications for efforts to treat AIDS and prevent its spread.

For one, the findings point up the need to develop new drugs for AIDS therapy. "If it [AZT resistance] turns out to have a clinically relevant correlate, we will have to develop alternatives, or use drug combinations," Anthony Fauci, the director of the National Institute of Allergy and Infectious Diseases, said in an interview with *Science*. Several potential AIDS drugs are being evaluated in clinical trials, but are not yet widely available to patients. The people taking AZT currently number in the thousands, perhaps in excess of 20,000, according to a spokeswoman for the Burroughs Wellcome Co.

Moreover, as many as 1.5 million people in the United States may have been infected by the AIDS virus, but have not yet developed the full-blown immunodeficiency syndrome. Clinical trials to determine whether AZT can delay or prevent the development of AIDS have been started. The discovery of the drug-resistant virus variants raises the possibility that, even if the progression of the disease can be postponed, the virus that ultimately produces symptoms might not be so readily controlled by AZT. Also worrisome is the possibility that the resistant AIDS virus variants might be transmitted to more people.

The AZT-resistant viruses were identified by Brendan Larder and Graham Darby of Wellcome Research Laboratories in Kent, England, and Douglas Richman of the University of California, San Diego, and the San Diego Veterans Administration Medical Center. The researchers obtained isolates of the AIDS virus, which goes by the scientific name of human immunodeficiency virus 1 (HIV-1), from patients who had been taking AZT for varied lengths of time up to 30 months and from patients who had never received the drug.

The isolates from 5 of the 15 patients who had been on the drug for more than 6 months were markedly—as much as 100 times—more resistant to the growth inhibitory effects of AZT than isolates from untreated patients and from those who had taken the drug for less than 6 months, Larder says. Moreover, two or more sequential isolates had been obtained from a few patients, and these showed that the AIDS virus becomes progressively more resistant to AZT as time goes on. The way in which the AIDS virus acquires the resistance is currently unknown.

At present, there is no direct evidence linking the development of AZT resistance to a worsening of the patients' symptoms. The patients producing the resistant HIV-1 variants did not, for example, show increased blood concentrations of the viral antigen p24. This suggests that virus reproduction had not gone up in the patients.

Clinicians often find, however, that the condition of AIDS patients begins to deteriorate within 6 to 18 months after they begin taking the drug. "The drug is clearly effective. The responses in many people are dramatic, but they are short-lived," says Jerome Groopman of New England Deaconess Hospital in Boston. "It's terribly important to know what the biological basis of the clinical progression is." The development of AZT resistance is one possible cause, but not the only one.

Larder points out that the current study,

FDA Approval of HIV Medicines

1981: First AIDS cases are reported in the United States.

'85-'89

1987
Zidovudine (NRTI)

'90-'94

1991
Didanosine (NRTI)

1992
Zalcitabine (NRTI)

1994
Stavudine (NRTI)

'95-'99

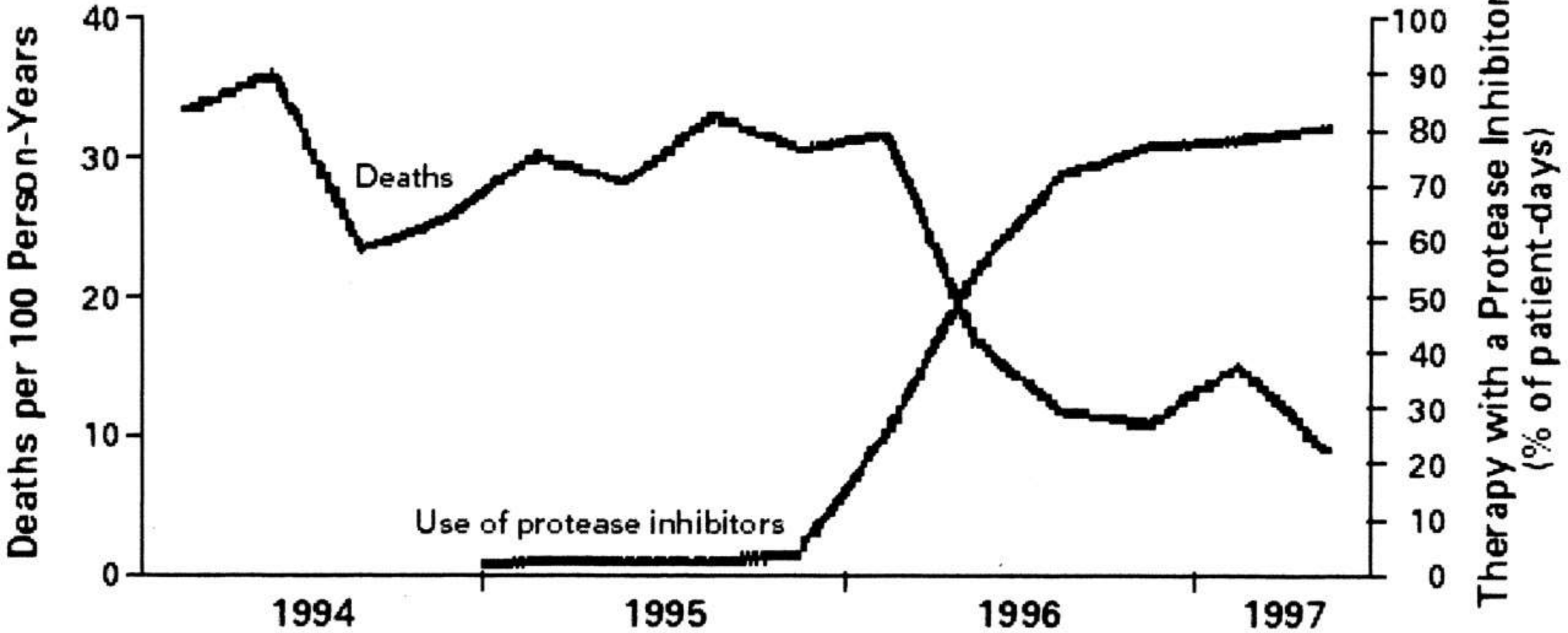
1995
Lamivudine (NRTI)
Saquinavir (PI)

1996
Indinavir (PI)
Nevirapine (NNRTI)
Ritonavir (PI)

1997
Combivir (FDC)
Delavirdine (NNRTI)
Nelfinavir (PI)

1998
Abacavir (NRTI)
Efavirenz (NNRTI)

1999
Amprenavir (PI)



Palella, F, et al. NEJM. 1998; 338: 853-860.

Great strides have been made in the goals and delivery of ART over 30 years

1987

Goal: Delaying disease progression

2020s

Goal: Maximal virologic suppression with improved quality of life

ZDV monotherapy

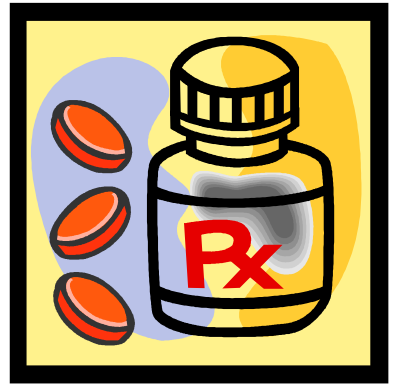
Triple-drug ART with multiple pills

Highly effective and tolerable
2 and 3-drug ART single-tablet regimens
Once monthly maintenance option


Past
Present
Future

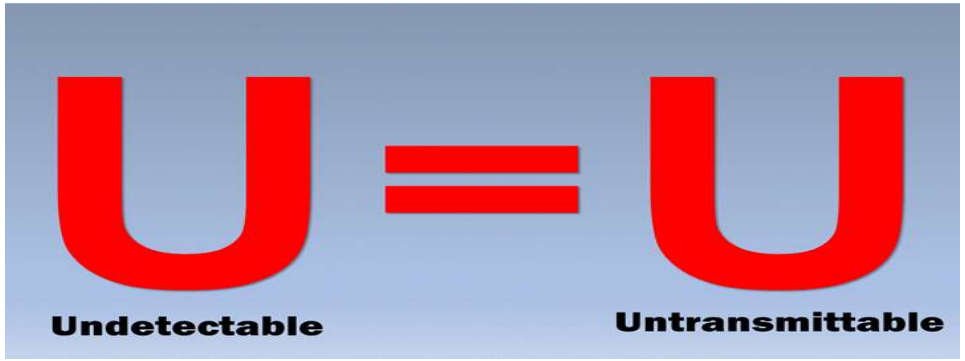
Classes of Antiretrovirals

- Entry Inhibitors
  - Attachment inhibitor
  - Post-attachment inhibitor
  - CCR5 co-receptor blocker
  - Fusion inhibitor
- Capsid Inhibitor (newly approved)
- Reverse Transcriptase inhibitors
  - Nucleoside reverse transcriptase inhibitors
  - Non-nucleoside reverse transcriptase inhibitors
- Integrase inhibitors
- Protease inhibitors



Goals of ART

- Maximum and durable viral suppression to prevent resistance, treatment failure, and opportunistic infections.
- Restoration/preservation of the immune system.
- Reduction of HIV morbidity/mortality.
- Improvement in quality of life.
- Prevent transmission of HIV transmission.

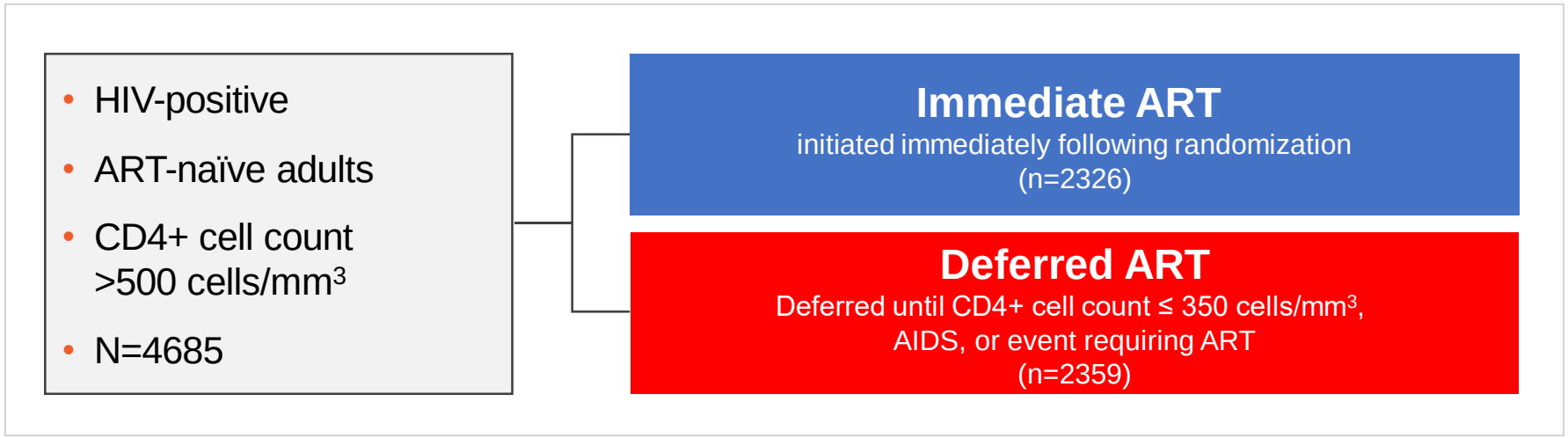


Critical Questions

- When to start?
- What to start?

START led to global consensus that all PWH should start ART, regardless of CD4 count

- **Global guideline committees have "recommended ART for all people with HIV, regardless of CD4+ T lymphocyte cell count, to reduce the morbidity and mortality associated with HIV infection" and "to prevent HIV transmission" [1-5]**



- **4.1% vs 1.8% in deferred vs immediate arms experienced serious AIDS or non-AIDS–related event or death (HR: 0.43; 95% CI: 0.30-0.62; *P*<0.001)**
- **Serious AIDS events, TB, and several cancers increased in deferred arm**

1. WHO Guidelines 2021. 2. US DHHS Adult Guidelines 2021. 3. Saag MS, et al. *JAMA*. 2020;324(16):1651-1669.
4. EACS Guidelines 11.0. 2021. 5. BHVA Guidelines 2016. 6. The INSIGHT START Study Group. *N Engl J Med.* 2015;373:795-807.

Worldwide consensus on when to start ART

Guideline Organization	Who Should Receive ART
World Health Organization [1]*	• ART should be initiated for all PWH at any WHO clinical stage and any CD4+ cell count
US DHHS [2]	• ART is recommended for all persons with HIV, regardless of CD4+ T lymphocyte cell count
IAS-USA [3]	• ART is recommended for all adults with HIV infection
EACS [4]*	• Starting ART is recommended for all PWH regardless of CD4 count
British HIV Association [5]*	• Recommend people with HIV start ART

*Changed recommendation based on results of START trial.

1. WHO Guidelines 2021.
2. US DHHS Adult Guidelines 2022.
3. Gandhi RT, et al. 2022.
4. EACS Guidelines 12.0. 2023.
5. BHVA Guidelines 2022.

How to Construct an Initial Regimen

NRTI Backbone + Anchor Drug

TAF or TDF plus FTC or 3TC
OR
ABC/3TC

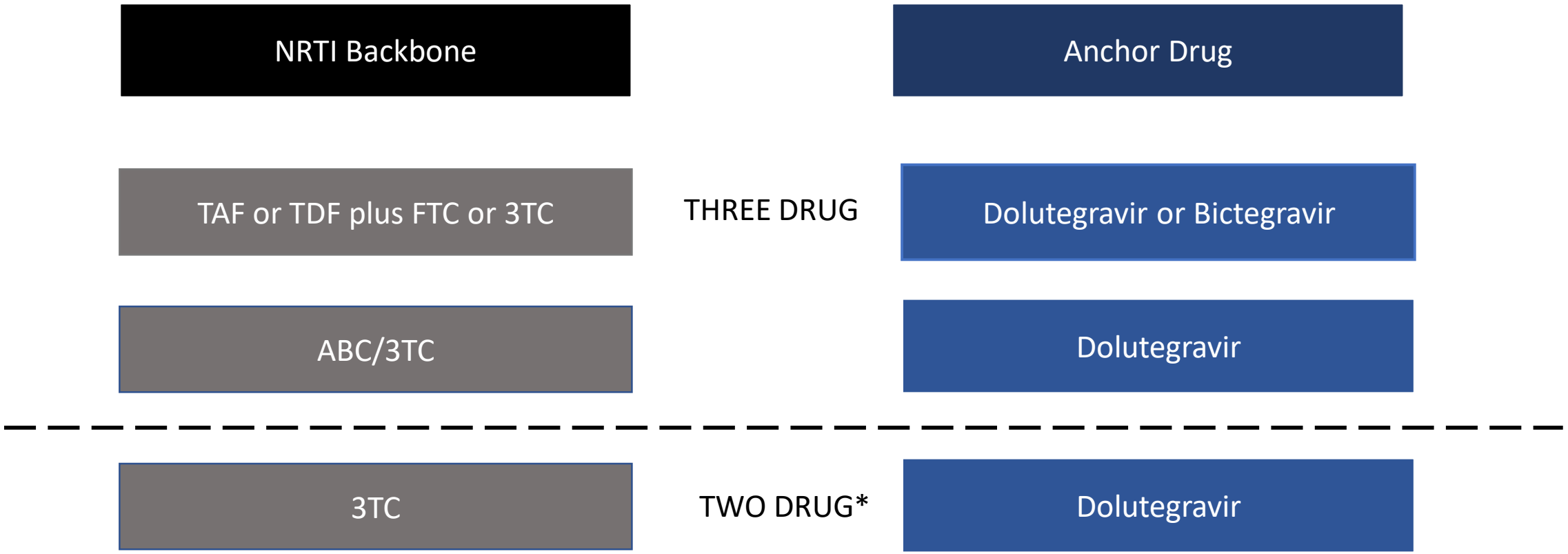
High barrier to resistance

- Boosted PIs or dolutegravir or bictegravir
- Especially important for adherence concerns
- Often ok even if 3TC or FTC resistance

Low barrier to resistance

- Most NNRTIs, raltegravir or elvitegravir
- MUST HAVE fully active backbone
- Less good if adherence concerns

First Line Regimens, 2024



*Not for VL > 500,000, concurrent hepatitis B infection or before confirmation that all drugs are active

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv

DHHS, IAS-USA Guidelines: Recommended Regimens for First-line ART

- Current ART options reflect the **most effective** and **most well tolerated** regimens ever available as a result of more than 2 decades of continued incremental improvements

DHHS[1]	IAS-USA[2]
Recommended initial regimens for most people with HIV: ▪ BIC/FTC/TAF ▪ DTG/ABC/3TC, if HLA-B*5701 negative ▪ DTG + (TAF or TDF)/(3TC or FTC) ▪ DTG/3TC, except for individuals with HIV-1 RNA > 500,000 c/mL, with HBV, or for whom results of HIV genotypic resistance testing or HBV testing are not yet available	*Generally recommended initial regimens:* ▪ BIC/FTC/TAF ▪ DTG plus: ▪ TAF/FTC, TDF/FTC, TDF/3TC ▪ DTG/3TC with caveats

1. DHHS Guidelines. September 2022. 2. Gandhi. JAMA. 2022

Long Acting Injectable

- January 2021 LA Cabotegravir and Rilpivirine was approved for **monthly** injections as a switch option
- February 2022 LA Cabotegravir and Rilpivirine was approved for **every other month** injections as a switch option

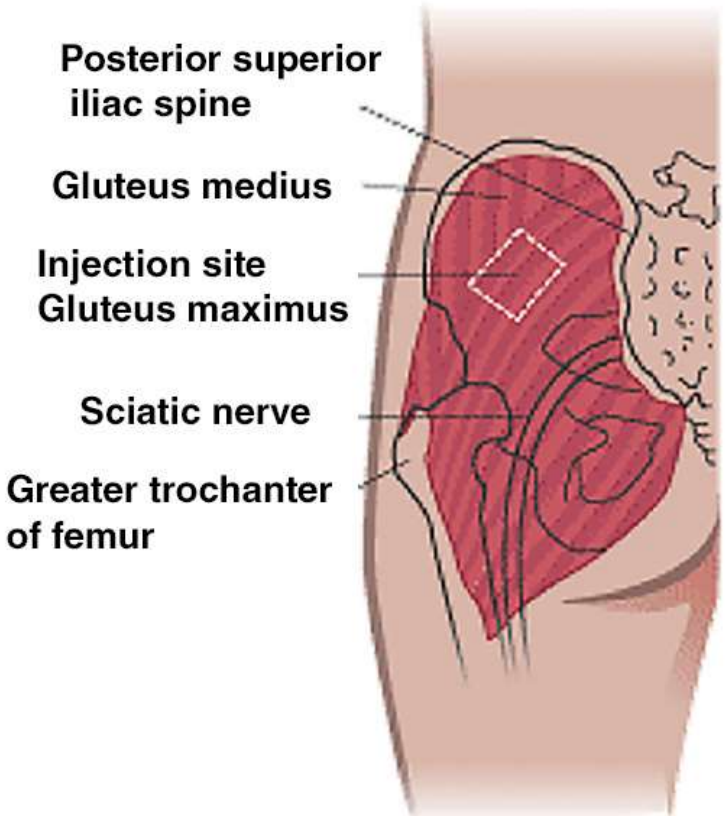
Indication

- Cabenuva is indicated as a complete regimen for the treatment of HIV in adults to replace the current antiretroviral (ART) regimen in those who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable ART regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.

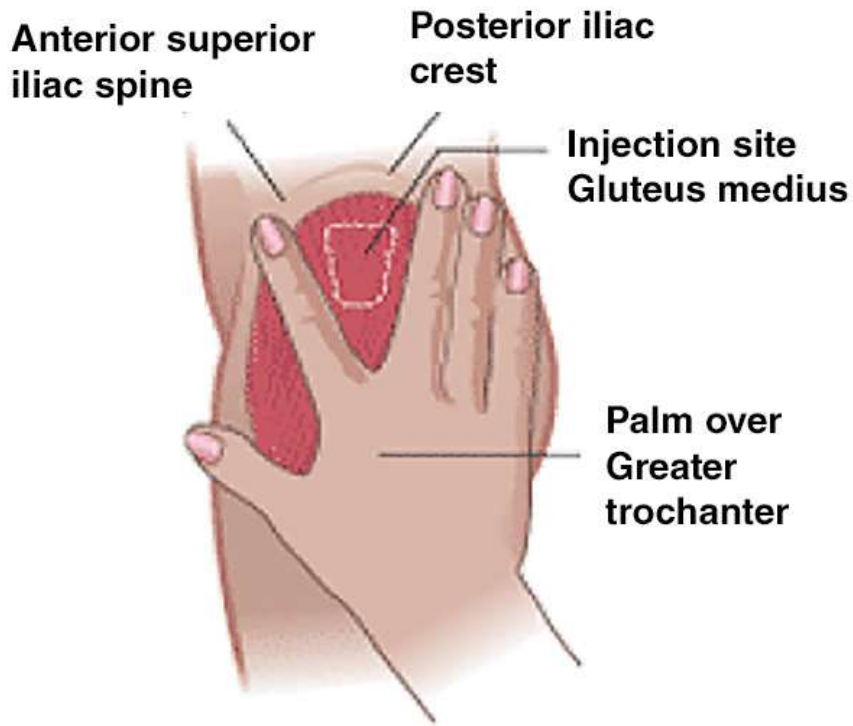
Injections

- Administer each injection at separate gluteal injection sites (opposite sides or 2 cm apart) during the same visit.
- The ventrogluteal site is recommended (see next slide).
- Use Z-track technique.
- Box supplied with 23g 1 ½ inch needle
- If the patient has a BMI > 30 kg/m^2 a longer needle may be required (up to 3 inches)

Dorsogluteal Site



Ventrogluteal Site



Injection Site reactions (through week 48)

Patient Reported Outcomes

- <u>Participants in ATLAS and FLAIR:</u>
  - High degree of satisfaction
  - High degree of acceptance
  - High degree of tolerability
  - Preference for long acting injectables

Murray, et al. AIDS and Behavior. 2020. 24:3533-3544


PAST
FUTURE

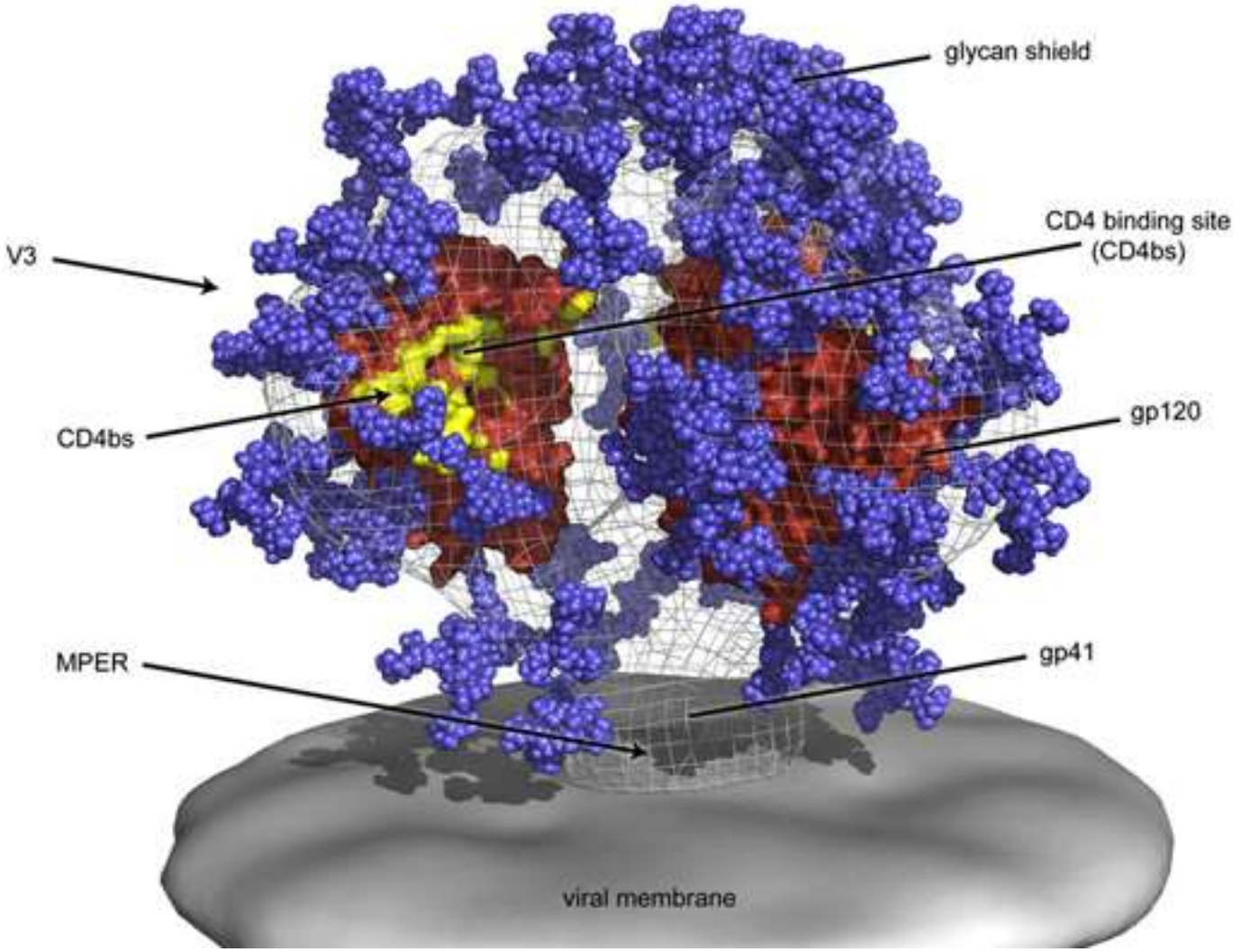
Categories

- Broadly neutralizing antibodies (bNAbs)
- Longer acting injectables (Ultra long acting injectables)
- Once weekly oral treatment options
- Self administered injections

Broadly Neutralizing antibodies

Neutralizing antibodies target HIV-1 Env

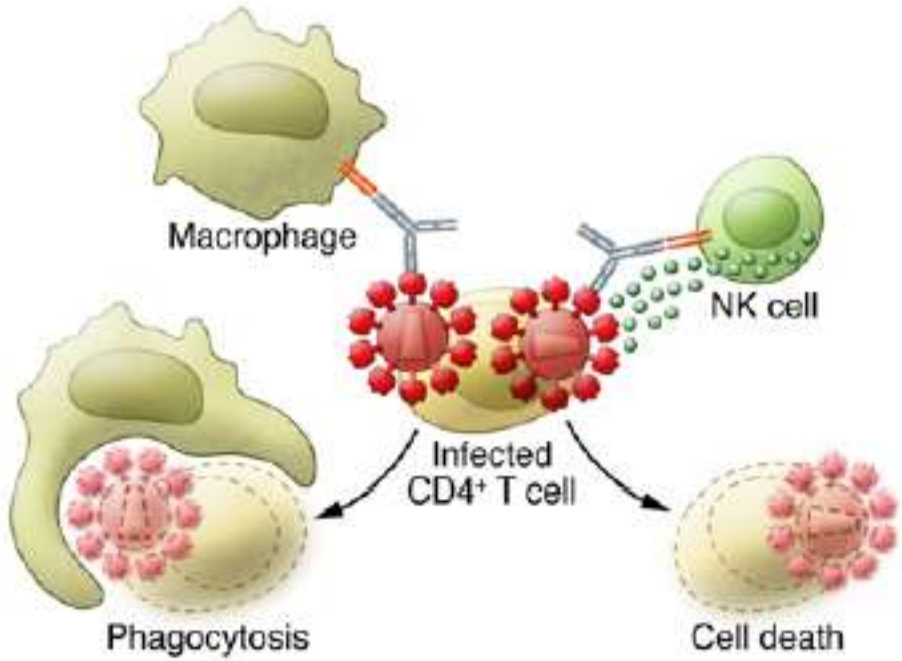
- Env covered in glycan shield
- Exposed regions of Env are highly variable
- Conserved epitopes are recessed, masked or transiently exposed
- Ab responses hampered by immune dysfunction



bNAb: mechanisms of action

Neutralization of cell-free virus

Controls viremia via above mechanisms, including prevention of cell-to-cell transmission, and virus release



Binding of virus-infected cells: ADCC via NK cells or ADCP phagocytosis via macrophages, CDC via complement

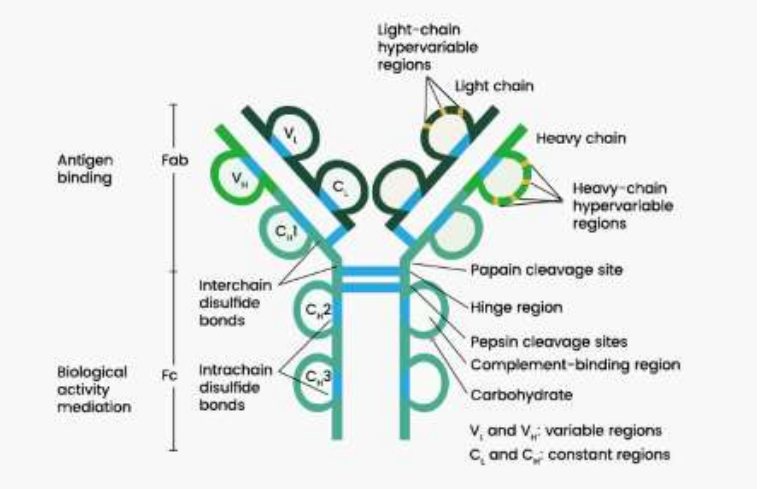
Halper-Stromberg and Nussenzweig JCI 2015; Duffoo et al. Nat Comm 2022; Malbec et al. J Exp Med 2013

bNAb Properties: potential advantages over ART

1. **Long acting**

   $T_{1/2}$ ~extended:

   Mutations in Fc affect binding to neonatal Fc receptor



Sinobiological

2. **Low toxicity**
   - mAb therapy generally well tolerated
3. ***Killing of infected cells***
   - Additional mechanism of action compared to smART
   - Clearance of free virus and clearance of HIV-infected cells
4. ***Immunomodulation***
   - Engage with host immune system to boost responses

Longer Acting Injectables

Enhanze (rHuPH20)

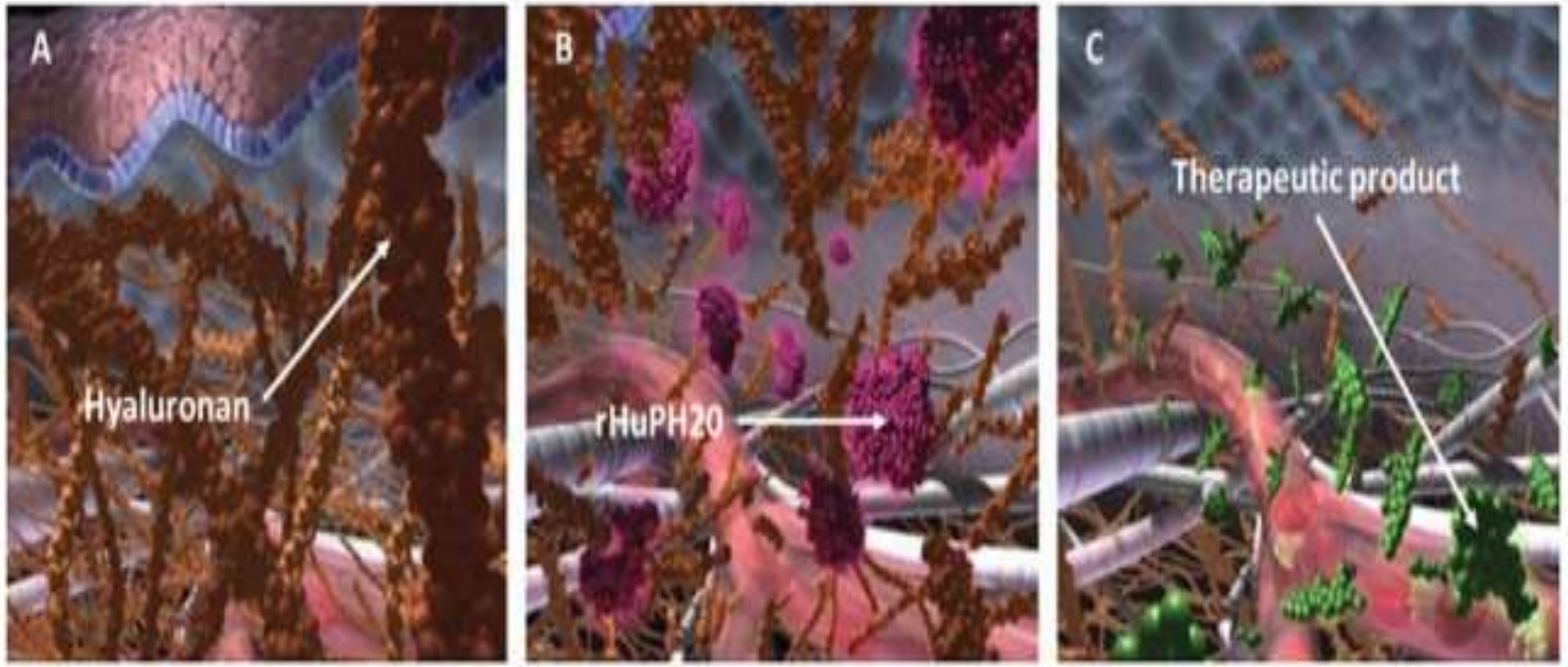
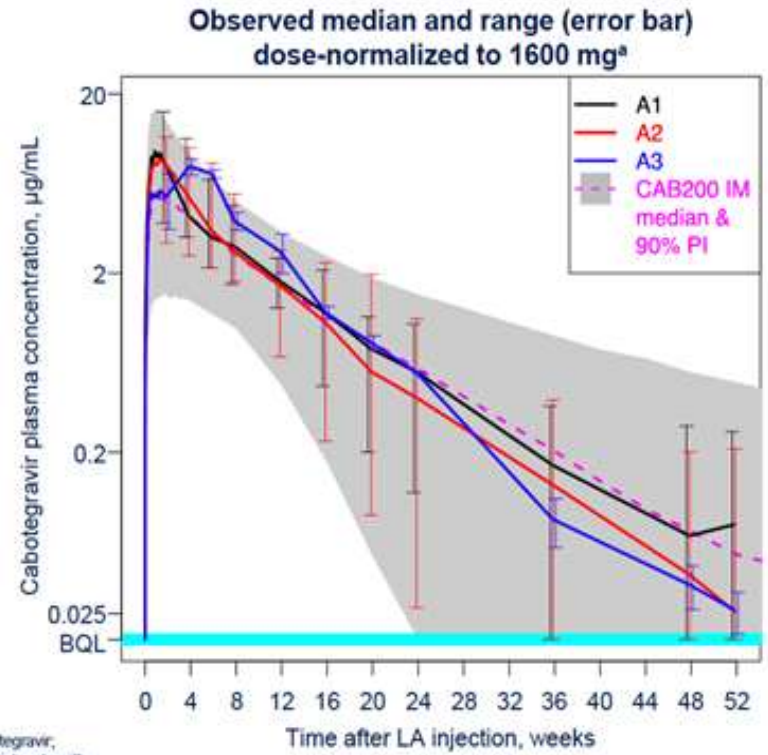


Figure 1. rHuPH20 mechanism of action. (A) Hyaluronan creates a resistance to bulk fluid flow and limits large volume SC drug delivery, dispersion, and absorption. (B) rHuPH20 depolymerizes hyaluronan, (C) facilitating SC bulk fluid flow and increasing the dispersion and absorption of co-administered therapeutics.

Part A: Pharmacokinetics of CAB200 + rHuPH20

Parameter, geometric mean (%CVb)	Part A: CAB200 SC + rHuPH20		
	A1: 800 mg (4 mL) (n=10)	A2: 1600 mg (8 mL) (n=9)	A3: 3200 mg (16 mL) (n=2)
$AUC_{0-\infty}$, mg·h/mL	6.1 (27.9)	11.5 (28.7)	26.6 (8.9)
Cmax, µg/mL	4.7 (47.4)	7.7 (46.2)	16.2 (10.1)
$t_{1/2}$, days	54.6 (57.9)	47.9 (68.5)	42.3 (5.3)
tmax, hours	164 (40.0)	316 (62.6)	755 (39.4)

- $t_{1/2}$ was similar to CAB200 IM, indicating similar overall absorption rate[1,2]
- Cmax was higher than CAB200 IM, indicating faster initial absorption[2]
- Exposure increased with dose proportionally
- $AUC_{0-\infty}$ was higher than CAB200 IM, indicating potentially increased bioavailability[2]



$AUC_{0-\infty}$, area under the plasma concentration–time curve from 0 to infinity; BQL, below quantification limit of 0.025 µg/mL; CAB, cabotegravir; Cmax, maximum observed plasma concentration; %CVb, coefficient of variation; IM, intramuscular; LA, long-acting; n, number of participants with valid PK parameters; PI, prediction interval; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous; $t_{1/2}$, terminal half-life; tmax, time to Cmax.
[a]Error bars before Week 2 are not displayed for visibility. **1.** Han et al. *Br J Clin Pharmacol.* 2022;88:4607-4622. **2.** Cabenuva [prescribing information]. ViiV Healthcare; 2023.

Part A: Safety of CAB200 + rHuPH20

The overall tolerability/safety profile, along with PK considerations, led to a decision not to progress this dosing strategy:

- Non-ISR drug-related AEs were infrequent
- ISRs occurred in all participants (22/22); ISR grade increased with increasing CAB dose
  - Most common ISRs were injection site pain, erythema, swelling, and warmth
- A single drug-related SAE was reported: 1 participant who received CAB 3200 mg (16 mL) SC + rHuPH20 experienced injection site erythema with necrosis requiring wound care; the wound completely healed, and the erythema resolved by Day 105

	Part A: CAB200 SC + rHuPH20		
Parameter	**A1: 800 mg (4 mL) (N=10)**	**A2: 1600 mg (8 mL) (N=10)**	**A3: 3200 mg (16 mL) (N=2)**
Any ISR, n (%)	10 (100)	10 (100)	2 (100)
Total ISR events, n	45	48	11
Maximum grade 1, n (% of ISRs)	25 (56)	29 (60)	5 (45)
Maximum grade 2, n (% of ISRs)	20 (44)	16 (33)	1 (9)
Maximum grade ≥3, n (% of ISRs)	0	3 (6)	5 (45)[a,b]
Duration, median (IQR), days[c]	9 (7-37)	24 (7-138)	28 (15-105)

AE, adverse event; CAB, cabotegravir; IQR, interquartile range; ISR, injection site reaction; PK, pharmacokinetics; rHuPH20, recombinant human hyaluronidase PH20; SAE, serious AE; SC, subcutaneous.
[a]1 drug-related SAE of injection site erythema with necrosis. [b]No further participants were dosed in A3 due to the safety findings from these 2 sentinel participants. [c]Only calculated for events that have resolved (A1: 45/45 [100%], A2: 45/48 [94%]; A3: 11/11 [100%]).

New Ultra-Long-Acting Formulation CAB-ULA

Part C: PK of New Ultra-Long-Acting Formulation CAB-ULA

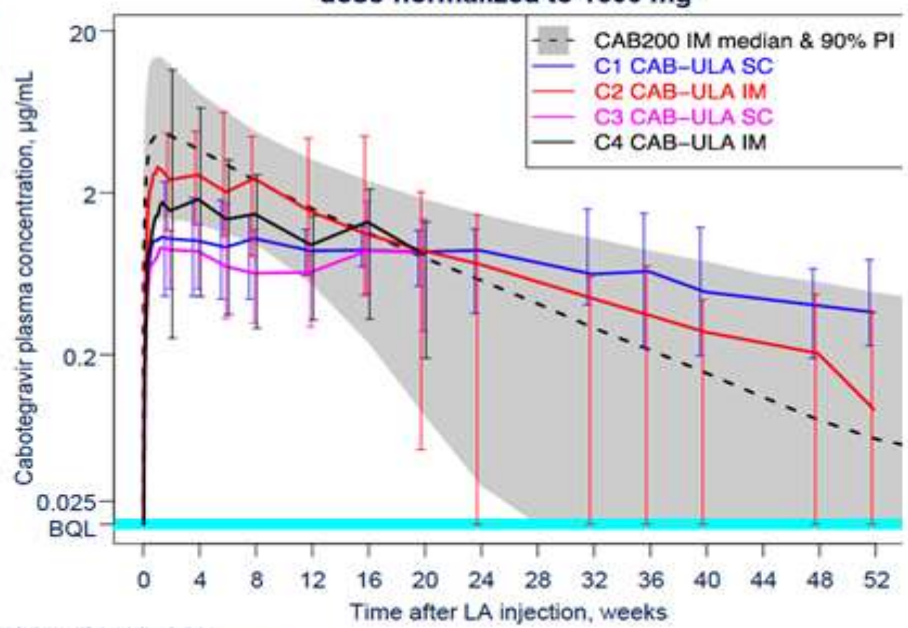
Part C: CAB-ULA

Parameter, geometric mean (%CVb)	SC C1 800 mg (2 mL) (n=8)	SC C3 1200 mg (3 mL) (n=8)	IM C2 800 mg (2 mL) (n=8)	IM C4 1200 mg (3 mL) (n=8)
Cmax, µg/mL	0.7 (35.5)	0.8 (39.0)	1.8 (53.5)	1.8 (148)
tmax, hours	570 (158)	349 (147)	298 (136)	383 (107)

CAB-ULA has slower absorption and longer $t_{1/2}$ than CAB200 IM

- PK profiles were flatter than CAB200 IM
- CAB-ULA Cmax was lower with SC than IM; both were lower than CAB200 IM[1]
- tmax was longer than CAB200 IM[1]
- **CAB-ULA $t_{1/2}$ for SC and IM was predicted to be >6x and >2x the $t_{1/2}$ of CAB200 IM, respectively[1,a]**

Observed median and range (error bar) dose-normalized to 1600 mg[b]



BQL, below quantification limit of 0.025 µg/mL; CAB, cabotegravir; Cmax, maximum observed plasma concentration; %CVb, coefficient of variation; IM, intramuscular; n, number of participants with valid PK parameters; PI, prediction interval; PK, pharmacokinetics; SC, subcutaneous; $t_{1/2}$, terminal half-life; tmax, time to Cmax; ULA, ultra-long-acting. [a]Current follow-up time is insufficient to calculate final $t_{1/2}$ value for CAB-ULA. [b]Error bars before Week 2 are not displayed for visibility. **1.** Cabenuva [prescribing information]. ViiV Healthcare; 2023.

Part C: Safety of CAB-ULA

- Non-ISR drug-related AEs were infrequent
- CAB-ULA IM was better tolerated than SC
  - SC: ISRs occurred in 100% (16/16) of participants; most common SC ISRs were erythema, nodule, and pain
  - IM: ISRs occurred in 69% (22/32) of participants; most common IM ISR was pain and except for 1, all were mild (grade 1)
- CAB-ULA IM ISR profile appears comparable to established CAB200 IM ISR profile despite higher single doses of CAB-ULA

	Part C: CAB-ULA				
	SC		IM		
Parameter	C1: 800 mg (2 mL) (N=8)	C3: 1200 mg (3 mL) (N=8)	C2: 800 mg (2 mL) (N=8)	C4: 1200 mg (3 mL) (N=8)	C5: 1600 mg (3 mL) (N=16)
Any ISR, n (%)	8 (100)	8 (100)	3 (38)	8 (100)	11 (69)
Total ISR events, n	21	24	5	9	15
Maximum grade 1, n (% of ISRs)	19 (90)	22 (92)	4 (80)	9 (100)	14 (93)
Maximum grade 2, n (% of ISRs)	2 (10)	2 (8)	1 (20)	0	1 (7)
Maximum grade ≥3, n (% of ISRs)	0	0	0	0	0
Duration, median (IQR), days[a]	15 (6-41)	13 (6-21)	5 (5-8)	4 (3-5)	6 (4-8)

AE, adverse event; CAB, cabotegravir; IM, intramuscular; IQR, interquartile range; ISR, injection site reaction; SC, subcutaneous; ULA, ultra-long-acting.
[a]Only calculated for events that have resolved (C1: 15/21 [71%]; C3: 17/24 [71%]; C2: 5/5 [100%]; C4: 9/9 [100%]; C5: 12/15 [80%]).

Once weekly options

Islatravir + lenacapravir weekly

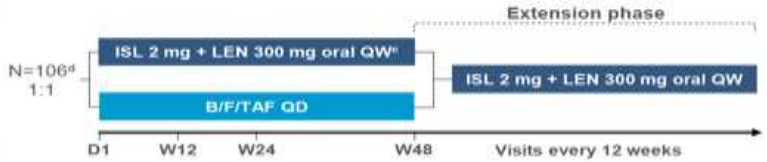
- Islatravir
  - Nucleoside reverse transcriptase translocation inhibitor
  - Prior studies have shown dose/ exposure-related decreases in CD4 and absolute lymphocyte counts
- Lenacapravir
  - First in class capsid inhibitor
- Both drugs have multiple mechanisms of action, potent ART activity at low doses and long half-lives that allow weekly dosing

Phase 2 study

Methods

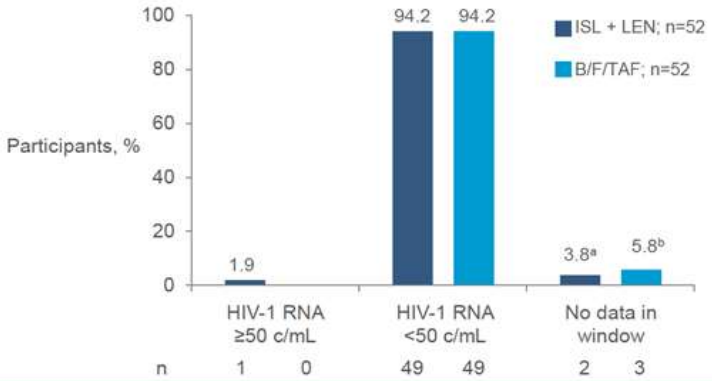
A Phase 2, open-label, active-controlled study in virologically suppressed PWH[a]

Inclusion criteria
- Aged ≥18 years
- Viral load <50 c/mL on B/F/TAF[b]
- No history of virologic failure
- CD4 count ≥350 cells/µl
- Lymphocytes ≥900 cells/µl
- No HBV infection



- **Primary endpoint:** Proportion with HIV-1 RNA ≥50 c/mL at Week 24 per FDA Snapshot algorithm
- **Secondary endpoints:**
  - Proportion with HIV-1 RNA ≥50 c/mL at Weeks 12 and 48
  - Proportion with HIV-1 RNA <50 c/mL at Weeks 12, 24, and 48
  - Change from Day 1 in CD4
  - Adverse events (AE) leading to study drug discontinuation
  - PK parameters[e]
- **Exploratory endpoints[e]:**
  - Treatment-emergent resistance to ISL and LEN
  - Participant-reported outcomes

Efficacy at Week 24



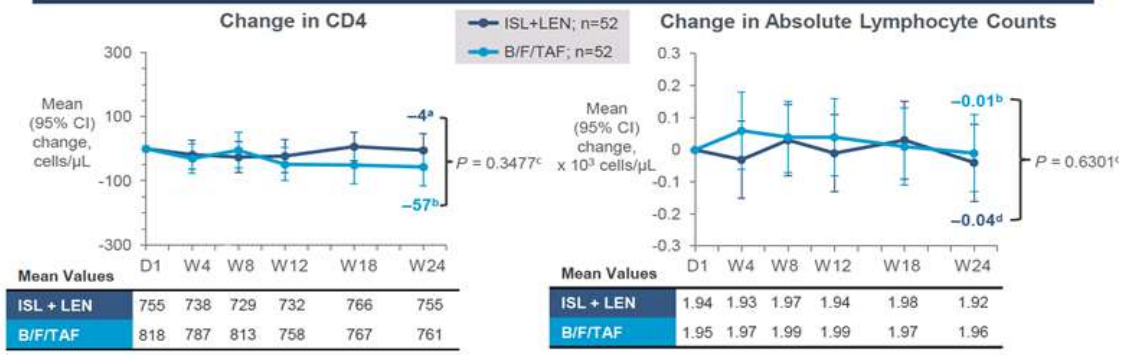
Participants in both treatment groups maintained high rates of virologic suppression

Grade 3/4 Laboratory Abnormalities

Participants with laboratory abnormalities, n (%)[a]	ISL + LEN (n=52)	B/F/TAF (n=52)
Grade 3	**5 (9.6)**	**4 (7.8)**
Increased ALT	1 (1.9)	0
Increased creatinine	1 (1.9)	0
Decreased creatinine clearance	2 (3.8)	2 (3.9)
Fasting hyperglycemia	0	1 (2.6)
Non-fasting hyperglycemia	1 (2.5)	2 (4.9)
Hyperkalemia	1 (1.9)	0
Glycosuria	1 (1.9)	2 (3.9)
Grade 4	**1 (1.9)**	**0**
Increased creatine kinase	1 (1.9)	0

No Grade 3 and 4 laboratory abnormalities were clinically significant, except ALT elevation seen in a participant with acute hepatitis B

CD4 and Absolute Lymphocyte Count Changes Through Week 24



Mean Values	D1	W4	W8	W12	W18	W24
ISL + LEN	755	738	729	732	766	755
B/F/TAF	818	787	813	758	767	761

Mean Values	D1	W4	W8	W12	W18	W24
ISL + LEN	1.94	1.93	1.97	1.94	1.98	1.92
B/F/TAF	1.95	1.97	1.99	1.99	1.97	1.96

- No between-group differences in CD4 and absolute lymphocyte count changes at Week 24
- No participants discontinued due to CD4 or absolute lymphocyte count decreases

Self administered Injections

Table 1: Select agents in development for HIV-1 Therapy (non-comprehensive)

DRUG	MANUFACTURER	DRUG CLASS	INDICATION	REGIMEN	ADMINISTRATION	DEVELOPMENT PHASE
ISL/DOR	Merck	NRTTI/NNRTI	VS	STR	QD, Oral	Phase III
ISL/LEN	Merck/Gilead	NRTTI/CA	VS	STR	QW, LA Oral	Phase II
LEN/BIC	Gilead	CA/InSTI	VS	STR	QD, Oral	Phase II
VH3810109	ViiV/GSK	bNAb	TBD	TBD	TBD, LA Injectable	Phase II
GS-6212	Gilead	InSTI	TBD	TBD	Q3M, LA Injectable	Phase I
GS-5894	Gilead	NNRTI	TBD	TBD	QW, LA Oral	Phase I
GS-1720	Gilead	InSTI	TBD	TBD	QW, LA Oral	Phase I
VH3739937	ViiV/GSK	MI	TBD	TBD	TBD, LA Injectable	Phase I
VH4524184	ViiV/GSK	InSTI	TBD	TBD	Q3M+, LA Injectable	Phase I

ARV, antiretroviral drug; BIC, bictegravir; bNAb, broadly-neutralizing antibody; CA, capsid inhibitor; DOR, doravirine; InSTI, integrase strand transfer inhibitor; LA, long acting; LEN, lenacapavir; MI, maturation inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NRTTI, nucleoside reverse transcriptase translocation inhibitor; PrEP, pre-exposure prophylaxis; QD, once daily; QW, once weekly; Q3M, once every 3 months; Q3M+, once every 3 months or more; STR, single-tablet regimen; TBD, to be determined; VS, virologically suppressed.

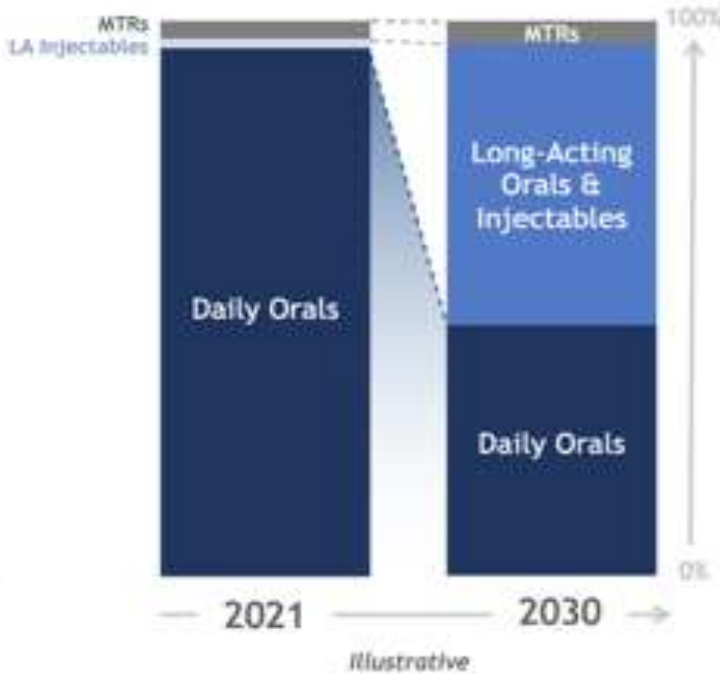
Diverse Pipeline of HIV Long-Acting Treatment Options

Modality	Frequency	Backbone		Partner	
Oral	Once-Daily	Lenacapavir	+	Bictegravir Phase 2/3 Combo	★
	1 Week	Lenacapavir	+	INSTI Oral Phase 1	★
		Lenacapavir	+	NNRTI Phase 1	
		Lenacapavir	+	Islatravir Phase 2[1]	
Injectable	3 Months	Lenacapavir	+	INSTI Inj. Phase 1	★
		Lenacapavir	+	NRTI Pre-IND	
	6 Months	Lenacapavir	+	INSTI 1 Pre-IND	★
		Lenacapavir	+	INSTI 2 Pre-IND	★
		Lenacapavir	+	2 bNAbs Phase 1b POC Combo	

★ Updated Disclosure

★ New Disclosure

Modality Mix Expected to be Driven by Gilead Innovation



Note: the combinations and dosing regimens shown are investigational and are not approved by any regulatory authority for any use; Their safety and efficacy are not established. Merck's islatravir is an investigational agent and is not approved by any regulatory authority for any use; its safety and efficacy are not established. 1. Lenacapavir + islatravir oral combo is expected to commence in 1H 2023. bNAbs - Broadly neutralizing antibody; IND - Investigational New Drug; INSTI - Integrase strand transfer inhibitor; LA - Long-acting; MTR - Multi-tablet regimen; NNRTI - Non-nucleoside reverse transcriptase inhibitor; NRTI - Nucleoside reverse transcriptase inhibitor; POC - Proof of concept.

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