UNIVERSITÀ DEGLI STUDI DI PADOVA

AZIENDA OSPEDALE UNIVERSITÀ PADOVA

Infezione da HIV: cosa ci riserva il futuro

Anna Maria Cattelan

Financial Disclosures

Gilead Sciences, ViiV Healthcare, Janssen-Cilag, MSD,
Menarini, Angelini, Pfizer

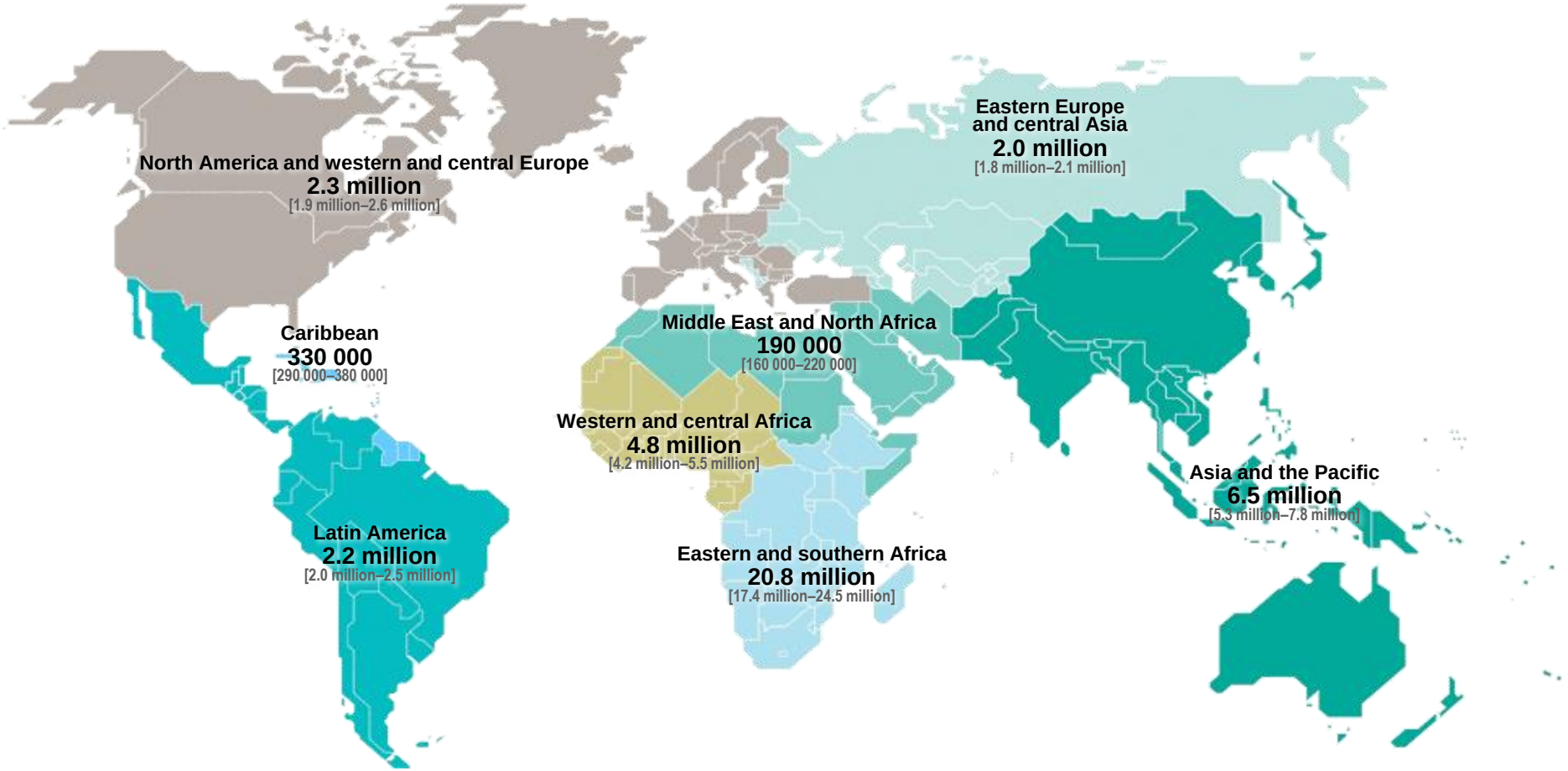
Agenda

Where we are

Where we are going to

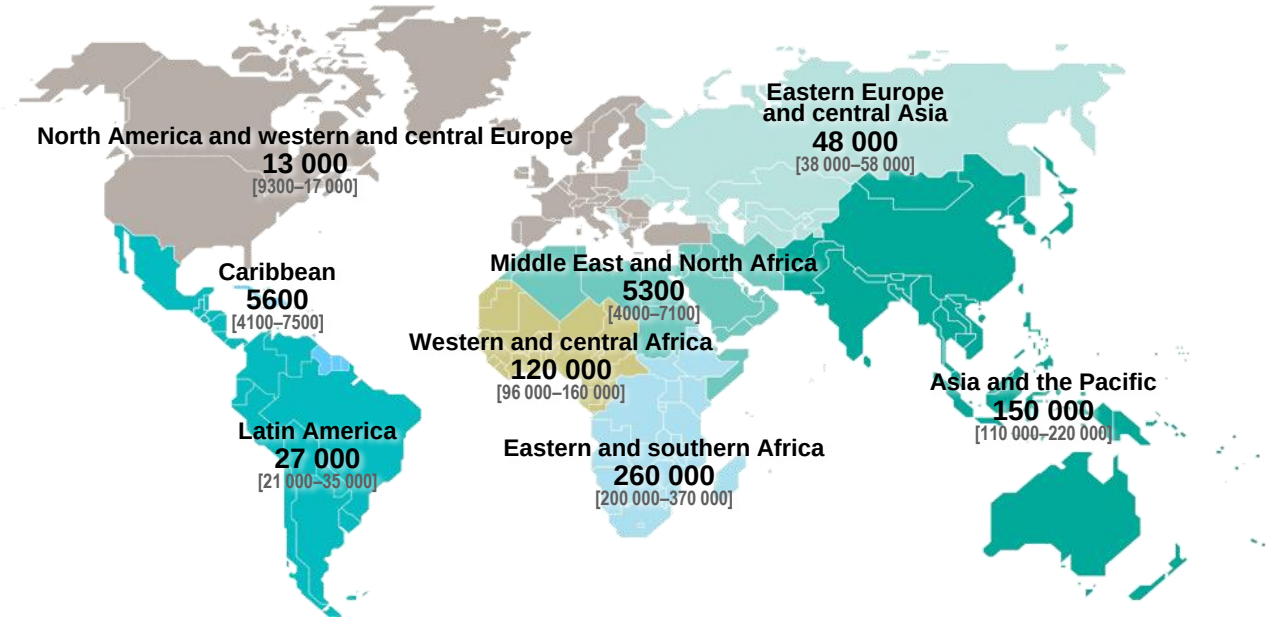
- ✓HIV epidemiology
- ✓HIV prevention
- ✓HIV therapy
- ✓HIV cure

Adults and children estimated to be living with HIV 2022



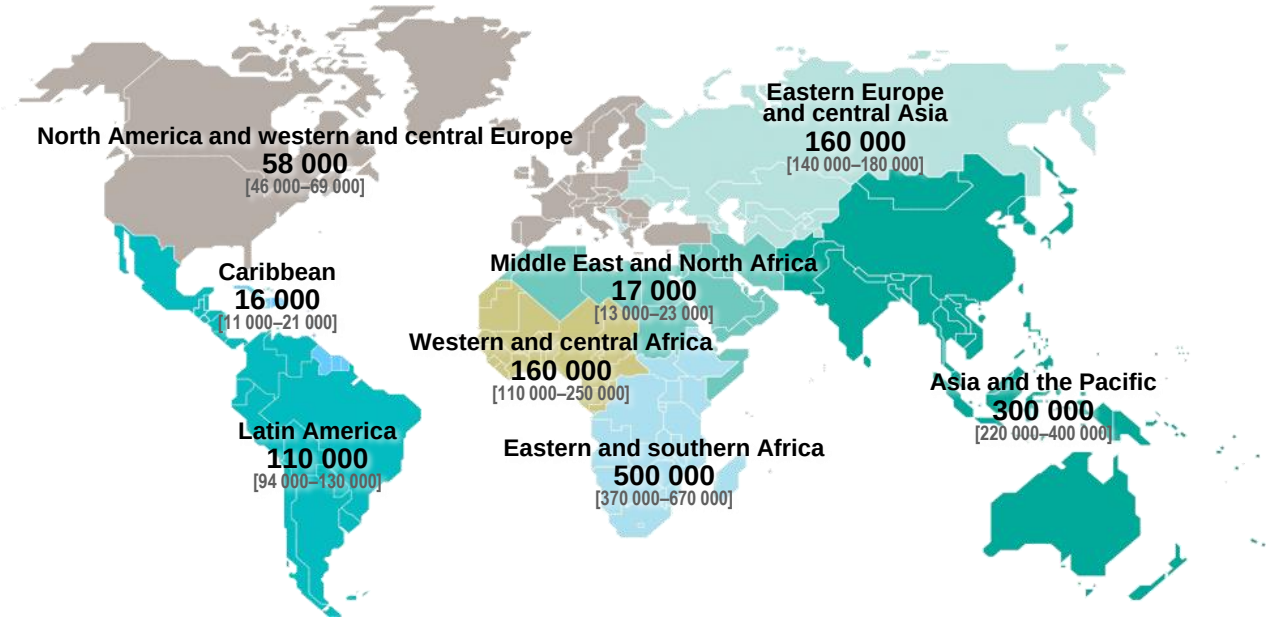
Total: 39.0 million [33.1 million–45.7 million]

Estimated adult and child deaths from AIDS | 2022



Total: 630 000 [480 000–880 000]

Estimated number of adults and children newly infected with HIV | 2022



Total: 1.3 million [1.0 million–1.7 million]

Table A: Characteristics of new HIV and AIDS diagnoses reported in the WHO European Region, the EU/EEA, and West, Centre and East of the WHO European Region, 2022

	WHO European Region	West	Centre	East	EU/EEA
Reporting countries/number of countries[a]	49/53	21/23	15/15	13/15	30/30
Number of HIV diagnoses	110 486	22 397	8 945	79 144	22 995
Rate of HIV diagnoses per 100 000 population	12.4	5.1	4.5	30.7	5.1
Percentage age 15–24 years	5.7%	8.9%	11.7%	4.2%	8.9%
Percentage age 50+ years	16.7%	21.8%	15.1%	15.5%	19.9%
Male-to-female ratio	1.8	2.4	2.9	1.6	2.4
Percentage of migrants[b]	26.7%	52.3%	27.0%	2.2%	48.3%
Transmission mode					
Sex between men	11.3%	35.2%	18.7%	3.7%	33.3%
Heterosexual transmission (men)	31.7%	15.1%	14.9%	38.3%	14.6%
Heterosexual transmission (women)	29.5%	21.0%	10.5%	34.1%	19.0%
Injecting drug use	16.1%	3.8%	2.1%	21.1%	4.3%
Mother-to-child transmission	0.6%	1.1%	0.8%	0.4%	1.2%
Unknown	10.8%	23.6%	52.8%	2.4%	27.3%
AIDS and late HIV diagnosis					
Percentage HIV diagnoses CD_4 <350 cells/mm^3	50.6	46.2	44.5	55.1	47.9%
Number of AIDS diagnoses[c]	7220	1873	825	4522	2349
Rate of AIDS diagnoses per 100 000 population	1.1	0.5	0.4	4.4	0.6

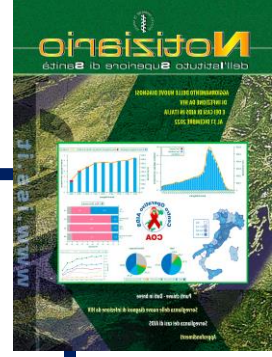
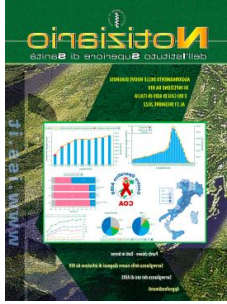
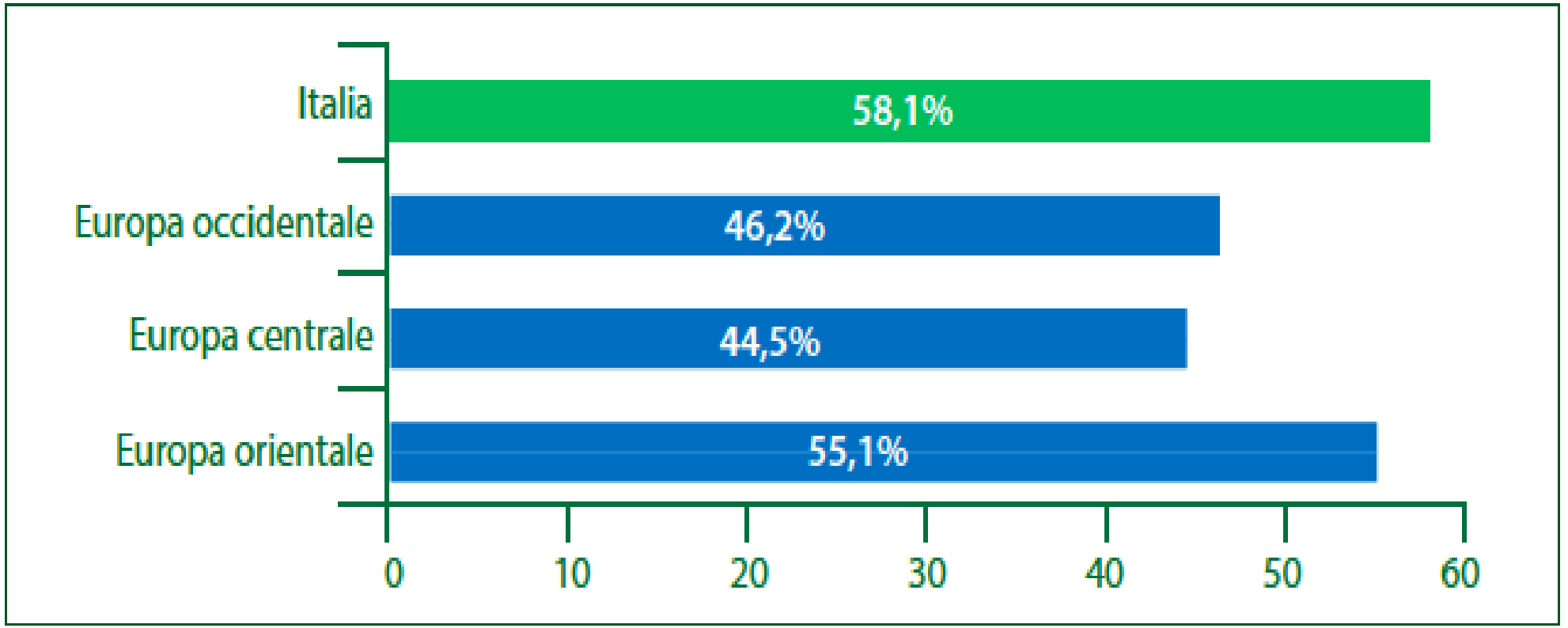


Tabella 1 - Nuove diagnosi di infezione da HIV (numero e variazioni % 2018-2022) per Regione di segnalazione e Incidenza per anno di diagnosi (2012-2022)

Regione	Anno inizio raccolta dati individuali	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	Variazioni percentuali 2019 vs 2018	2020 vs 2019	2021 vs 2020	2022 vs 2021	2022 vs 2019	Totale
Piemonte	1999	271	320	276	238	255	266	192	136	92	154	160	-29	-32	+67	+4	+18	2.360
Valle d'Aosta	2008	8	6	7	3	8	4	4	9	7	6	4	+125	-22	-14	-33	-56	66
Liguria	2001	108	77	97	115	116	116	99	74	72	61	60	-25	-3	-15	-2	-19	995
Lombardia	2009	1.103	997	879	872	779	740	691	560	119	243	218	-19	-79	+104	-10	-61	7.201
PA[a] di Trento	2010	39	23	24	15	33	24	20	30	19	6	4	+50	-37	-68	-33	-87	237
PA[a] di Bolzano	2010	17	18	20	15	19	15	4	7	8	4	11	+75	+14	-50	+175	+57	138
Veneto	2000	314	279	285	271	228	242	166	160	104	105	78	-4	-35	+1	-26	-51	2.232
Friuli Venezia Giulia	2010	71	65	76	47	54	48	27	46	28	29	30	+70	-39	+4	+3	-35	521
Emilia-Romagna	2006	436	345	377	323	329	312	252	244	168	203	206	-3	-31	+21	+1	-16	3.195
Toscana	2009	296	326	333	291	353	280	233	185	154	158	156	-21	-17	+3	-1	-16	2.765
Umbria	2009	67	57	61	56	54	59	42	38	38	27	24	-10	0	-29	-11	-37	523
Marche	2007	85	60	88	72	118	95	64	58	25	49	43	-9	-57	+96	-12	-26	757
Lazio	1985	645	618	622	554	586	521	463	351	227	323	293	-24	-35	+42	-9	-17	5.203
Abruzzo	2006	47	58	66	54	53	67	85	39	12	24	48	-54	-69	+100	+100	+23	553
Molise	2010	3	7	12	10	12	27	13	7	6	5	6	-46	-14	-17	+20	-14	108
Campania	2008	243	191	180	202	188	227	239	159	113	173	210	-33	-29	+53	+21	+32	2.125
Puglia	2007	131	133	121	147	169	194	155	162	86	91	130	+5	-47	+6	+43	-20	1.519
Basilicata	2010	13	5	14	16	17	18	7	8	0	6	12	+14	-100	n.c.[b]	+100	+50	116
Calabria	2009	9	12	24	30	17	12	9	4	0	11	7	-56	-100	n.c.[b]	-36	+75	135
Sicilia	2009	186	201	229	236	281	282	215	201	109	143	157	-7	-46	+31	+10	-22	2.240
Sardegna	2012	88	60	63	58	54	61	49	26	19	29	31	-47	-27	+53	+7	+19	538
Totale		**4.180**	**3.858**	**3.854**	**3.625**	**3.723**	**3.610**	**3.029**	**2.504**	**1.406**	**1.850**	**1.888**	**-17**	**-44**	**+32**	**+2**	**-25**	**33.527**
Incidenza per 100.000 residenti (calcolata per anno di diagnosi sulla popolazione residente)		7,0	6,4	6,4	6,0	6,2	6,0	5,1	4,2	2,4	3,1	3,2						



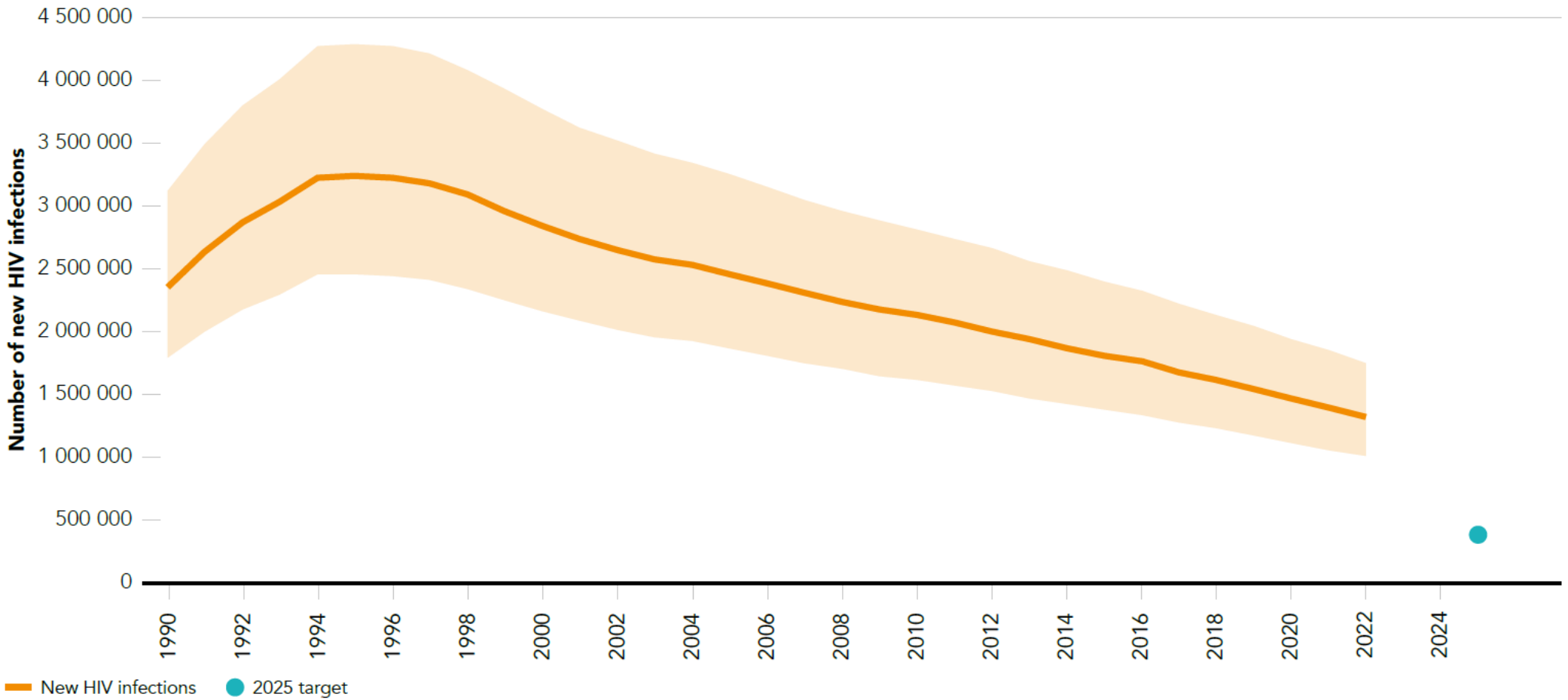
*Late presenters** 2022



(*) Late presenters: nuove diagnosi di infezione da HIV con numero di linfociti CD4 <350 cell/µl.

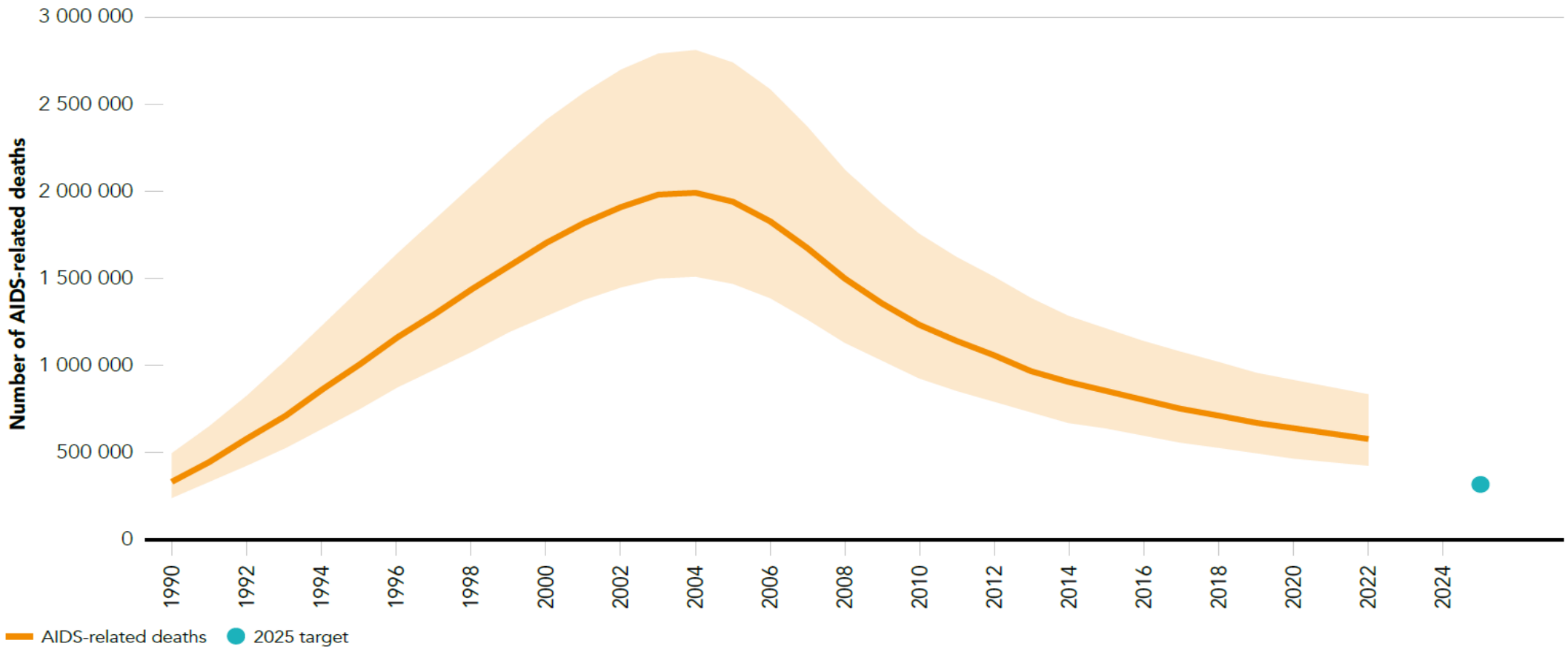
Fonti: Sistema di Sorveglianza HIV nazionale, *ECDC/WHO. HIV/AIDS Surveillance in Europe 2023-2022 data (1)*

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



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

Figure 12.2 Number of AIDS-related deaths, global, 1990–2022, and 2025 target



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

AMBITIOUS TARGETS AND COMMITMENTS FOR 2025

UNAIDS Global AIDS Update 2022
IN DANGER
IN DANGER
IN DANGER
IN DANGER
IN DANGER
IN DANGER
IN DANGER
IN DANGER
IN DANGER
IN DANGER

2025 HIV targets

10% **<** **END INEQUALITIES** **>** **95%**

LESS THAN 10%
LESS THAN 10% OF PEOPLE LIVING WITH HIV AND KEY POPULATIONS EXPERIENCE STIGMA AND DISCRIMINATION

LESS THAN 10%
OF PEOPLE LIVING WITH HIV, WOMEN AND GIRLS AND KEY POPULATIONS EXPERIENCE GENDER-BASED INEQUALITIES AND GENDER-BASED VIOLENCE

LESS THAN 10%
OF COUNTRIES HAVE PUNITIVE LAWS AND POLICIES

People living with HIV and communities at risk at the centre

95% OF PEOPLE AT RISK OF HIV USE COMBINATION PREVENTION

95%–95%–95% HIV TESTING, TREATMENT AND VIRAL SUPPRESSION AMONG ADULTS AND CHILDREN

95% OF WOMEN ACCESS SEXUAL AND REPRODUCTIVE HEALTH SERVICES

95% COVERAGE OF SERVICES FOR ELIMINATING VERTICAL TRANSMISSION OF HIV

90% OF PEOPLE LIVING WITH HIV RECEIVE PREVENTIVE TREATMENT FOR TUBERCULOSIS

90% OF PEOPLE LIVING WITH HIV AND PEOPLE AT RISK ARE LINKED TO OTHER INTEGRATED HEALTH SERVICES

UNAIDS

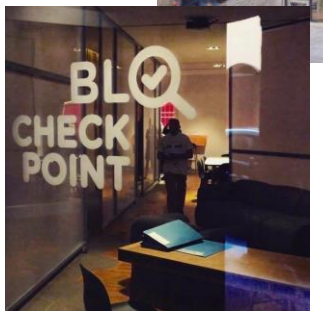
Implement accessibility to HIV testing

56 Dean Street

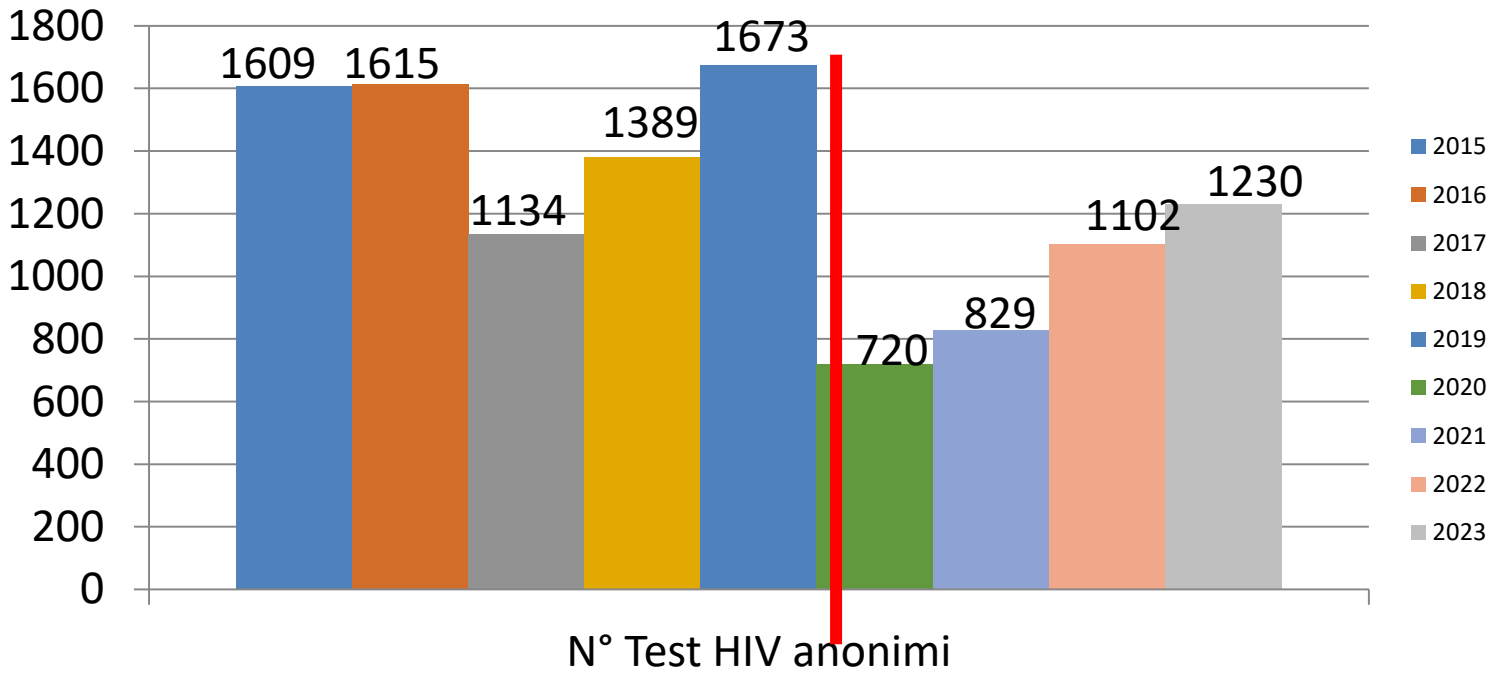
HIV opt-out testing in health care facilities

Mobile testing units

community outreach programs



Test HIV anonimi UOC Malattie Infettive-Padova



Età mediana: 35 anni (17-68); caucasici: 94%

Agenda

Where we are

Where we are going to

- ✓HIV epidemiology
- ✓**HIV prevention**
- ✓HIV therapy
- ✓HIV cure

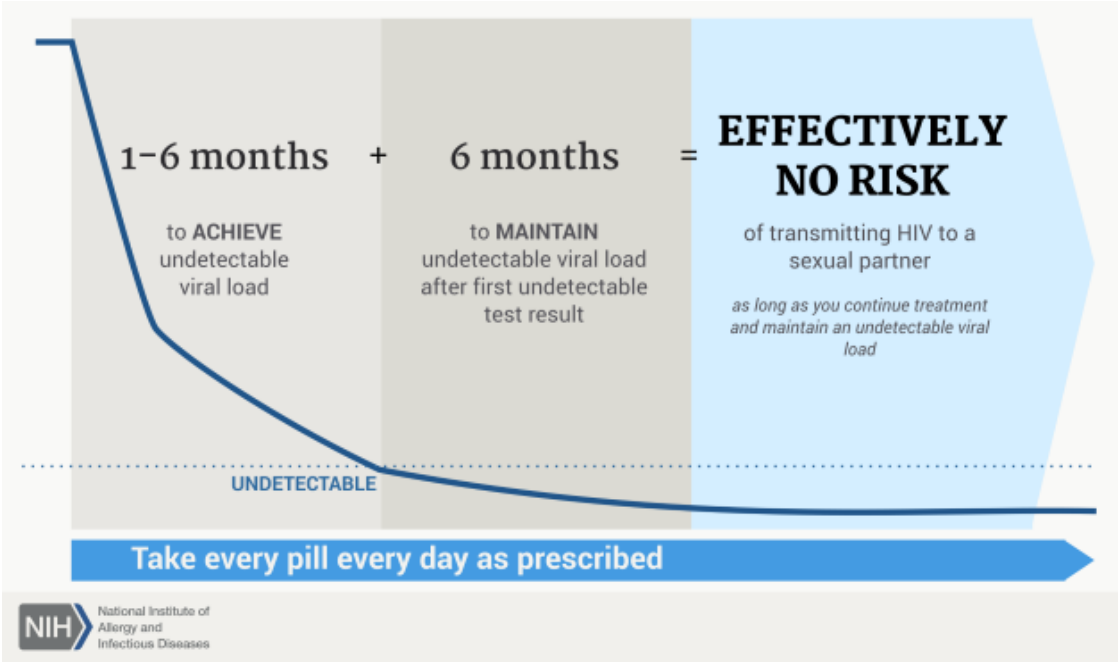
HIV Treatment as Prevention (TasP)

Last updated: November 8, 2023

Undetectable = Untransmittable

U=U

#UequalsU



- **U=U** signifies that achieving and maintaining HIV RNA levels <200 copies/mL with ART prevents HIV transmission through sex[1]
- Persons starting ART should use another form of prevention with sexual partners for at least the first 6 months of treatment and until an HIV RNA level of <200 copies/mL has been documented[1]
- **To maintain U=U** status, continue to take your medicines every day to help your viral load remain undetectable[2]

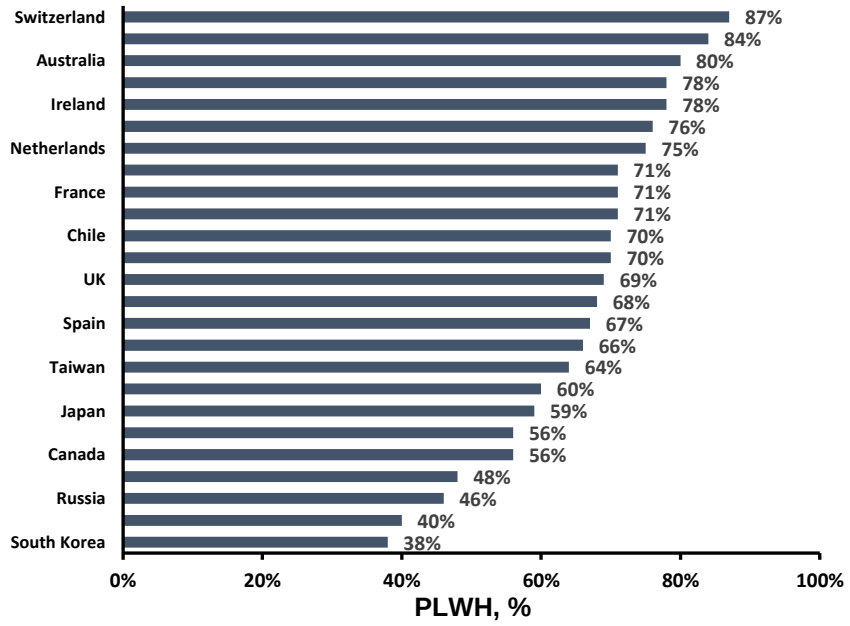
1. DHHS, December 2019. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. http://aidsinfo.nih.gov/guidelines. Accessed January 2020
2. Prevention Access Campaign. Undetectable = Untransmittable (U = U). http://www.preventionaccess.org. Accessed October 2019.

2019 Positive Perspectives Survey

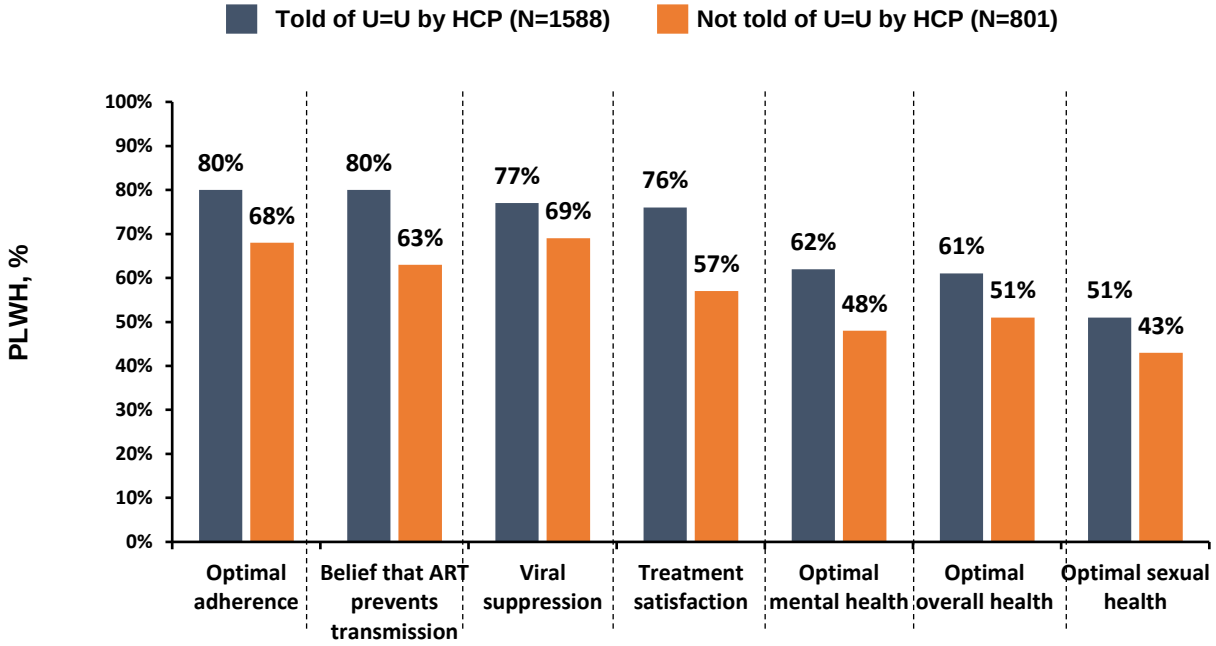
U=U Information-Sharing by Healthcare Providers

Cross-country analysis to investigate proportion PLWH informed of U=U by HCPs and association with PROs (April 2019-January 2020; N=2389)

Proportion Informed of U=U by HCPs, by Country



Association of Exposure to U=U Information and PROs



- **By country, proportion of PLWH informed of U=U by HCPs ranged widely from 38% to 87%**

- **PLWH who reported being informed of U=U by HCPs were more likely to report favorable PROs (all P<0.001)**

Intensified efforts by HCPs to better engage PLWH in U=U discussions may help improve adherence, viral suppression, treatment satisfaction and quality of life of PLWH

U=U, undetectable=untransmittable; PLWH, people living with HIV; HCPs, healthcare providers; PRO, patient-reported outcomes

Okoli C, et al. AIDS 2020. PED0773

Perceptions of U=U Among Italian Infectious Diseases Specialists: A Nationwide Survey on Providers' Attitudes Toward the Risk of HIV Transmission in Virologically Suppressed Patients

Diego Ripamonti,[1,*] Mariacristina Poliseno,[2,*] Giovanni Mazzola,[3] Pietro Colletti,[4] Antonio Di Biagio,[5] Benedetto Maurizio Celesia,[6] Andrea Gori,[7] Rita Bellagamba,[8] Giordano Madeddu,[9] Silvia Nozza,[10] Stefano Rusconi,[11] Antonio Cascio,[12] and Sergio Lo Caputo[2]

An **anonymous survey to 286 clinicians** to collect their opinions regarding six situations potentially at risk of HIV transmission between virologically suppressed patients and seronegative individuals who possibly require postexposure prophylaxis (PEP).

- ***51% of ID specialists deemed zero risk of HIV transmission through condomless sex for undetectable patients***. *This answer was more frequent among HIV specialists (30% vs. 21%, p = .01) and clinicians working in teaching hospitals (35% vs. 16%, p = .03).*
- *61% of participants would advise taking PEP for the HIV-negative partner in case of sexual intercourse with a seropositive person with a recent blip occurrence or absence of an HIV RNA test performed within the last 6 months (63%).*
- *73% of respondents deemed it essential to know patients' history of adherence to interpreting an HIV RNA test, regardless of its timing.*

When applying the U = U concept to daily clinical decisions, we observed an overall cautious attitude among physicians. Concerns mainly regarded the timing of the last HIV RNA test to the exposure event, especially in the absence of details on the patient's adherence. Wider diffusion and application of the U = U message are needed.

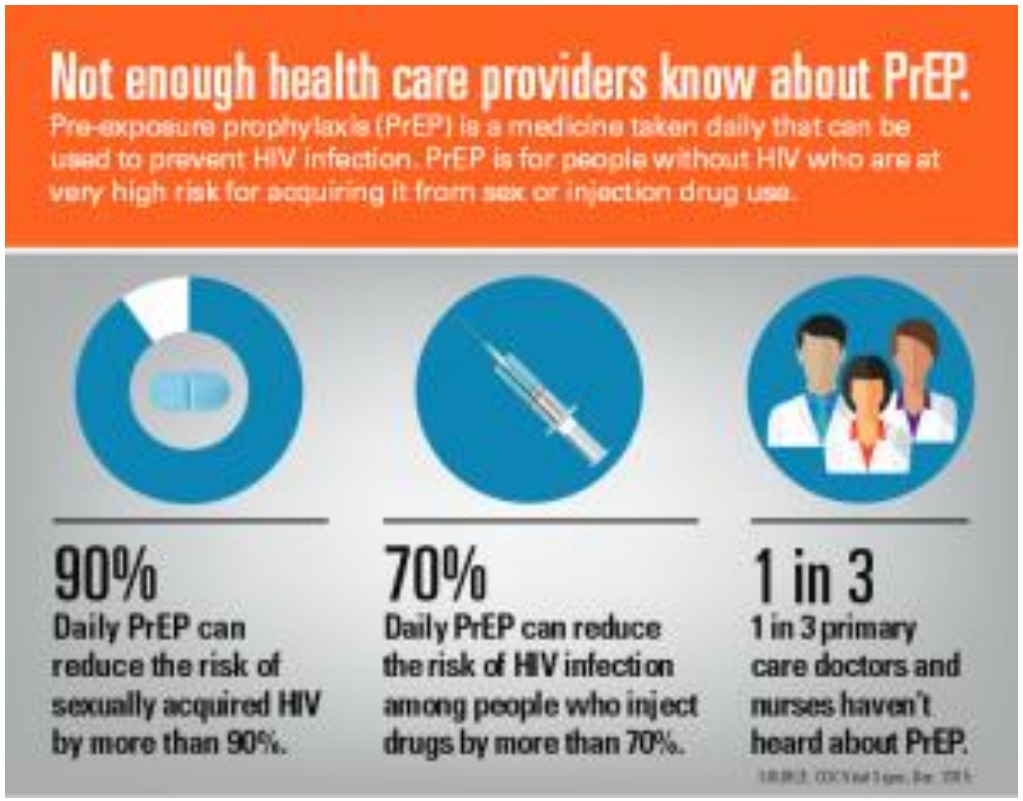
AIDS RESEARCH AND HUMAN RETROVIRUSES Volume 38, Number 11, 2022

PrEP is a daily medication taken to prevent HIV.

IS PREP RIGHT FOR YOU?

Urban Indian Health Institute

PrEP: Daily FTC/TDF

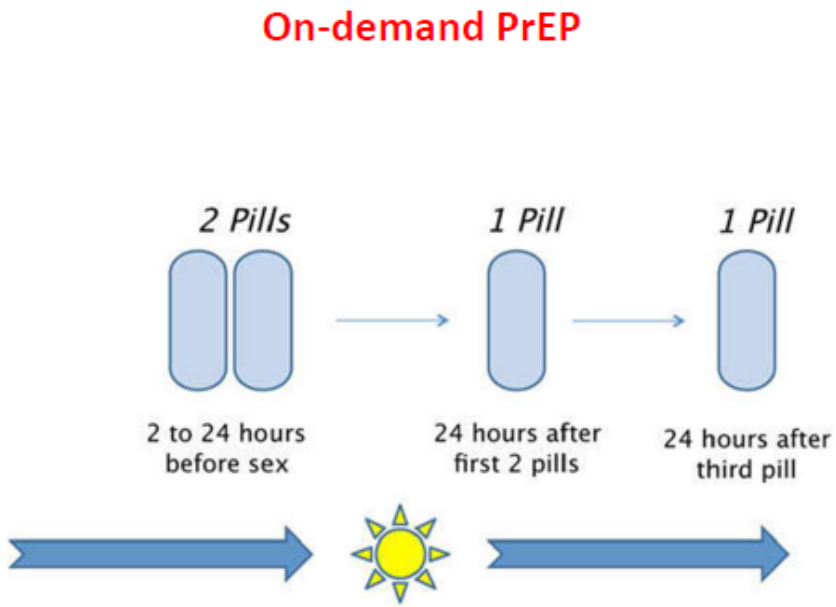


- FDA: daily oral FTC/TDF recommended for all adults and adolescents at risk for HIV through **sex or IDU**

On-Demand FTC/TDF Dosing Options for MSM

- FDA: daily oral FTC/TDF recommended for all adults and adolescents at risk for HIV through **sex or IDU**

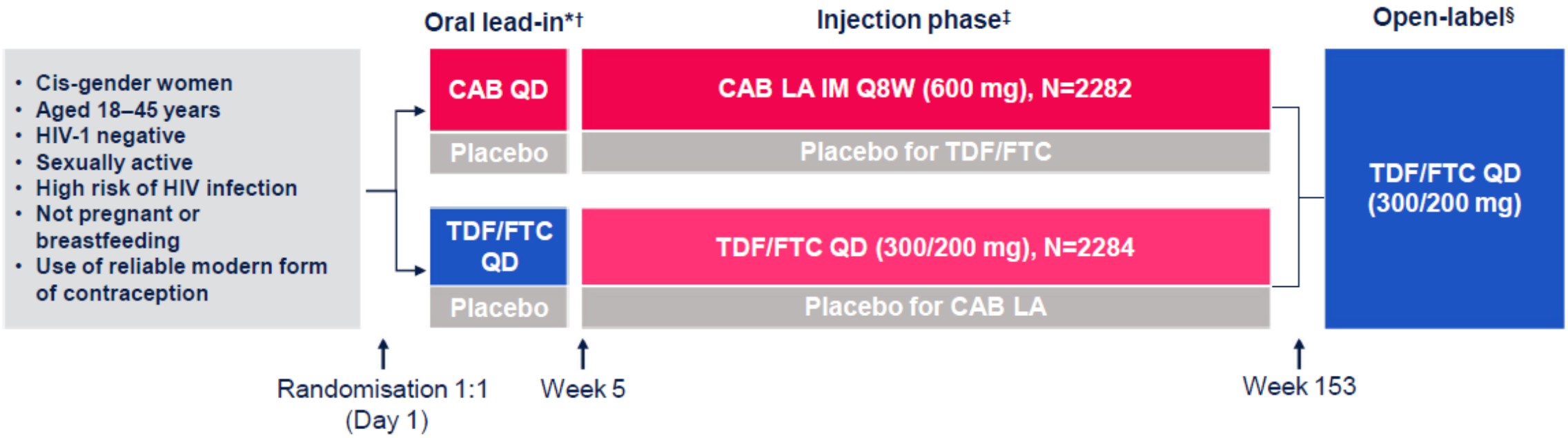
- WHO, IAS-USA, and Canadian guidelines include option of on-demand or event-driven (2:1:1) FTC/TDF dosing in MSM (off-label per FDA)



FTC/TDF PI. Saag. JAMA. 2020;324:1651. Tan. CMAJ. 2017;189:E1448.
WHO. apps.who.int/iris/bitstream/handle/10665/325955/WHO-CDS-HIV-19.8-eng.pdf.

New PrEP Options

Phase III, double-blind/double dummy study to evaluate the efficacy and safety of CAB LA Q8W vs daily oral TDF/FTC for PrEP in HIV-uninfected African cis-gender women:



Primary endpoints: Incident HIV infections during blinded comparison
Grade 2 or higher clinical and laboratory AEs

Delany-Moretlwe S, et al. HIVR4P 2021. Oral LB1479

New PrEP Options: Lenacapavir

Prevention Option(s):	Combination Prevention
Study Design:	Blind, Randomized
Arms and Assigned Interventions	

Description	Experimental: Blinded Phase: LEN + Placebo-to-match (PTM) F/TAF Participants will receive the following for at least 52 weeks: Subcutaneous (SC) lenacapavir (LEN) 927 mg every 26 weeks Oral PTM Emtricitabine/Tenofovir Alafenamide (F/TAF) once daily Oral LEN 600 mg on Days 1 and 2 Drug: Oral Lenacapavir (LEN) Tablets administered orally without regard to food Other Name: GS-6207 Drug: Subcutaneous (SC) Lenacapavir (LEN) Administered via SC injections Other Name: GS-6207 Drug: PTM F/TAF Tablets administered orally
Mode of Delivery	Subcutaneous, Tablet

Start Date	**End Date**
August 30, 2021	July 13, 2027

Enrollment:	5,010
Age range:	16 Years ↔ 25 Years
Population:	Cisgender Women

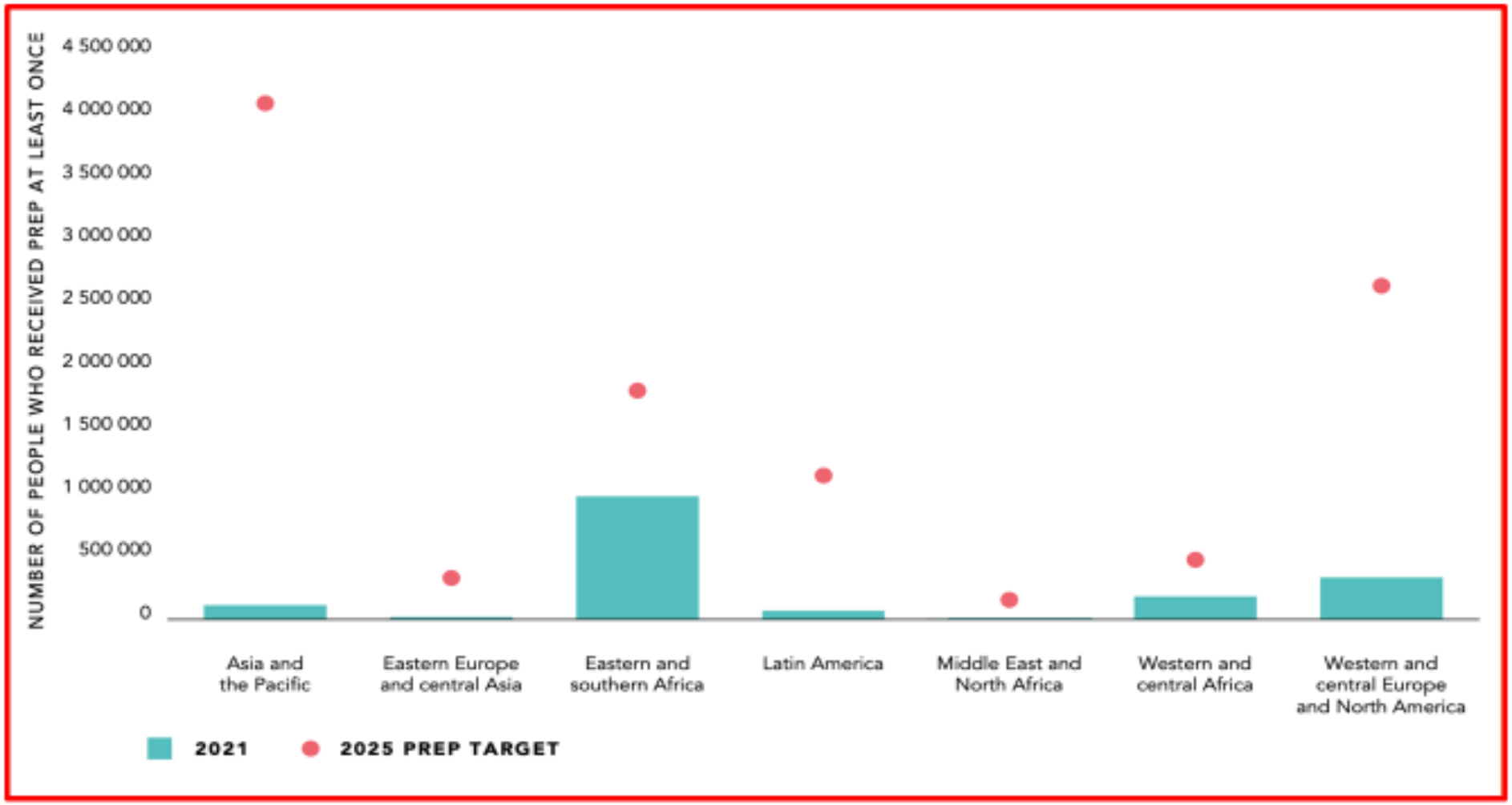
Sites

Madibeng Centre for Research
Brits
South Africa

Wits Reproductive Health and HIV Institute (Wits RHI)
Johannesburg
South Africa

UNAIDS

Number of people who received pre-exposure prophylaxis (PrEP) at least once during the reporting period, by region, 2021, and 2025 target



Agenda

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- ✓HIV epidemiology
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- ✓**HIV therapy**
- ✓HIV cure

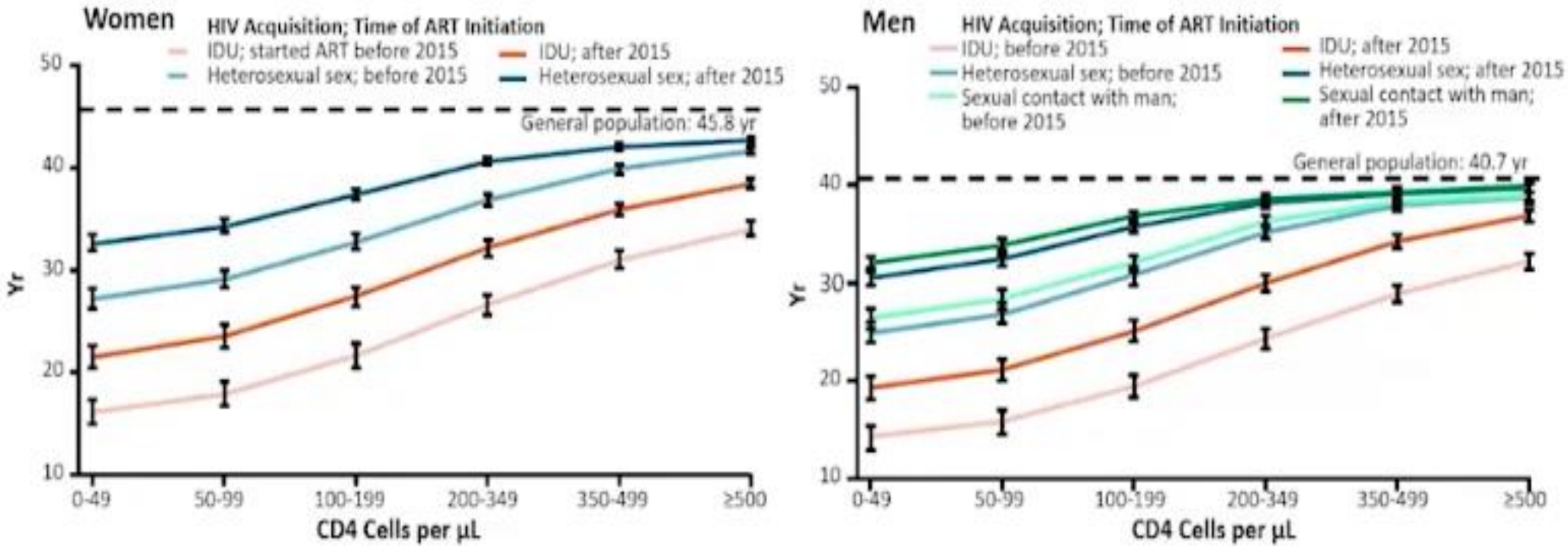
Antiretroviral therapy works great, and is getting better

1995 2006 2022

- ✓ more than 90% of patients on ART are stably suppresse
- ✓ 82% of patients on ART take STRs (ICONA data)
- ✓ excellent tolerability and low long-term toxicity

Estimated Life Expectancy of People living with HIV at Age 40 years

- Retrospective analysis of 206,891 participants aged ≥16 yr from 20 cohorts from Europe/North America



Based on 2015 estimates, a 20-yr-old person living with HIV who starts ART has 56.6 yr (if female) or 54.5 yr (if male) of life left

Lancet HIV 2023: 10; e295–307

HIV Medication Chart

Combination Antiretrovirals

Single-Tablet Regimens

- **Atripla**† (EFV/TDF/FTC)
- **Biktarvy** (BIC/TAF/FTC)
- **Complera** (RPV/TDF/FTC)
- **Delstrigo** (DOR/TDF/3TC)
- **Dovato** (DTG/3TC)
- **Genvoya** (EVG/COBI/TAF/FTC)
- **Juluca** (DTG/RPV)
- **Odefsey** (RPV/TAF/FTC)
- **Stribild** (EVG/COBI/TDF/FTC)
- **Symtuza** (DRV/COBI/TAF/FTC)
- **Triumeq** (DTG/ABC/3TC)

Long-Acting Injectable Regimens

- **Cabenuva** (CAB/RPV)

Regimens Used in Combination with Other HIV Medications

- **Combivir**† (ZDV/3TC)
- **Descovy** (TAF/FTC)
- **Epzicom**† (ABC/3TC)
- **Truvada**† (TDF/FTC)

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI)

- **Emtriva***† (emtricitabine, FTC)
- **Epivir***† (lamivudine, 3TC)
- **Viread***† (tenofovir DF, TDF)
- **Ziagen***† (abacavir, ABC)
- **Vemlidy** (tenofovir alafenamide, TAF) FDA approved for HBV only

Protease Inhibitors (PI)

- **Evotaz** (ATV/COBI)
- **Kaletra*** (lopinavir/ritonavir, LPV/RTV)
- **Prezcobix** (DRV/COBI)
- **Prezista*** (darunavir, DRV)
- **Reyataz***† (atazanavir, ATV)

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

- **Edurant** (rilpivirine, RPV)
- **Intelence**† (etravirine, ETR)
- **Pifeltro** (doravirine, DOR)
- **Sustiva**† (efavirenz, EFV)
- **Viramune***† (nevirapine, NVP)

Entry Inhibitors

- **Rukobia** (fostemsavir, FTR) gp120 Attachment Inhibitor
- **Selzentry*** (maraviroc, MVC) CCR5 Antagonist
- **Trogarzo** (ibalizumab, IBA) Post-Attachment Inhibitor

Boosting Agents

- **Norvir***† (ritonavir, RTV)
- **Tybost** (cobicistat, COBI)

Integrase Inhibitors (INSTI)

- **Isentress***▲ (raltegravir, RAL)
- **Isentress HD** (raltegravir, RAL)
- **Tivicay*** (dolutegravir, DTG)
- **Vocabria** (cabotegravir, CAB)

Global Recommended Initial ART Regimens

IAS-USA 2022[1]

For most PWH:

- **B/F/TAF**
- **DTG + F/TAF** or **TDF/(FTC** or **3TC)**
- **DTG/3TC***

For people with a history of CAB-LA† use as PrEP[1, 2]:

- Perform INSTI genotypic resistance testing before initiating ARV
- **DRV/c**¶ or **DRV/r** + (**TAF** or **TDF**)‡ + (**FTC** or **3TC**), pending results of genotype test

DHHS 2022[2]

For people with no history of CAB-LA† use as PrEP:

- **B/F/TAF**‡
- **DTG/ABC/3TC**
  If HLA-B*5701 negative and no chronic HBV coinfection
- **DTG** + (**TAF** or **TDF**)§ + (**FTC** or **3TC**)
- **DTG/3TC***

Each guideline notes that **INSTIs** and **TAF** have been associated with greater weight gain[1, 2, 3]

EACS 2022[3]

- **B/F/TAF**
- **DTG** + **ABC/3TC** or **DTG/ABC/3TC**
- **DTG** + **F/TAF** or **TDF**/(**FTC** or **3TC**)
- **RAL** + **F/TAF** or **TDF**/(**FTC** or **3TC**)
- **XTC** + **DTG** or **3TC/DTG**
- **DOR** + (**F/TAF** or **TDF/XTC**) or **TDF/3TC/DOR**

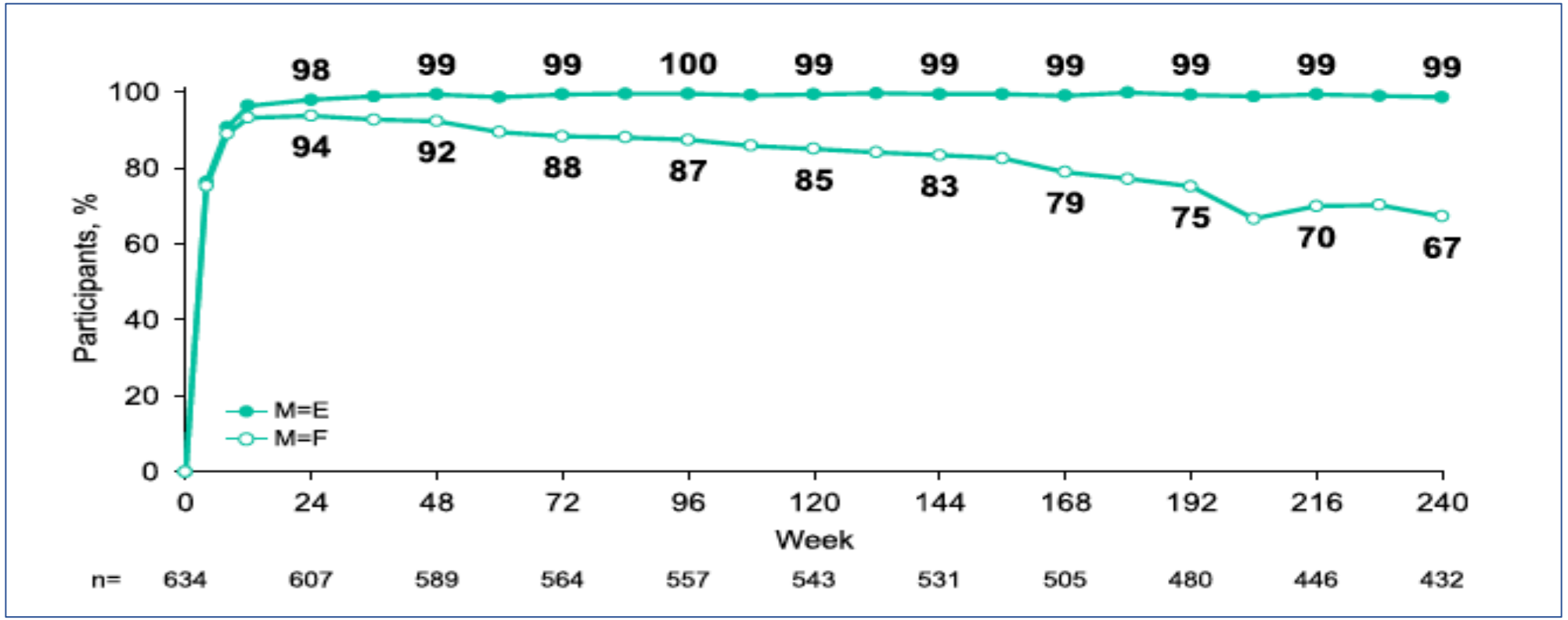
- Genotypic resistance testing recommended[1, 2, 3]:
  - At the time of diagnosis (ideally)
  - Before initiation of ARV
- If results of genotypic testing are unknown, first-line regimen should have high genetic barrier

Please see slide notes for footnotes. EACS, European AIDS Clinical Society; DHSS, Department of Health and Human Services; IAS, International Antiviral Society

1. Gandhi RT, et al. JAMA 2023;329:63-84; 2. DHHS. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf (accessed Oct. 20, 2022);
3. EACS. https://www.eacsociety.org/media/guidelines-11.1_final_09-10.pdf (accessed Nov. 22, 2022)

Bictegravir/emtricitabine/tenofovir alafenamide as initial treatment for HIV-1: five-year follow-up from two randomized trials

Paul E. Sax,[a,] José R. Arribas,[b] Chloe Orkin,[c] Adriano Lazzarin,[d] Anton Pozniak,[e] Edwin DeJesus,[f] Franco Maggiolo,[g] Hans-Jürgen Stellbrink,[h] Yazdan Yazdanpanah,[i] Rima Acosta,[j] Hailin Huang,[j] Jason T. Hindman,[j] Hal Martin,[j] Jared M. Baeten,[j] and David Wohl,[k] on behalf of the GS-US-380-1489 and GS-US-380-1490 study investigators*



No Treatment-Emergent Resistance Has Been Observed in B/F/TAF Clinical Trials

Clinical rial

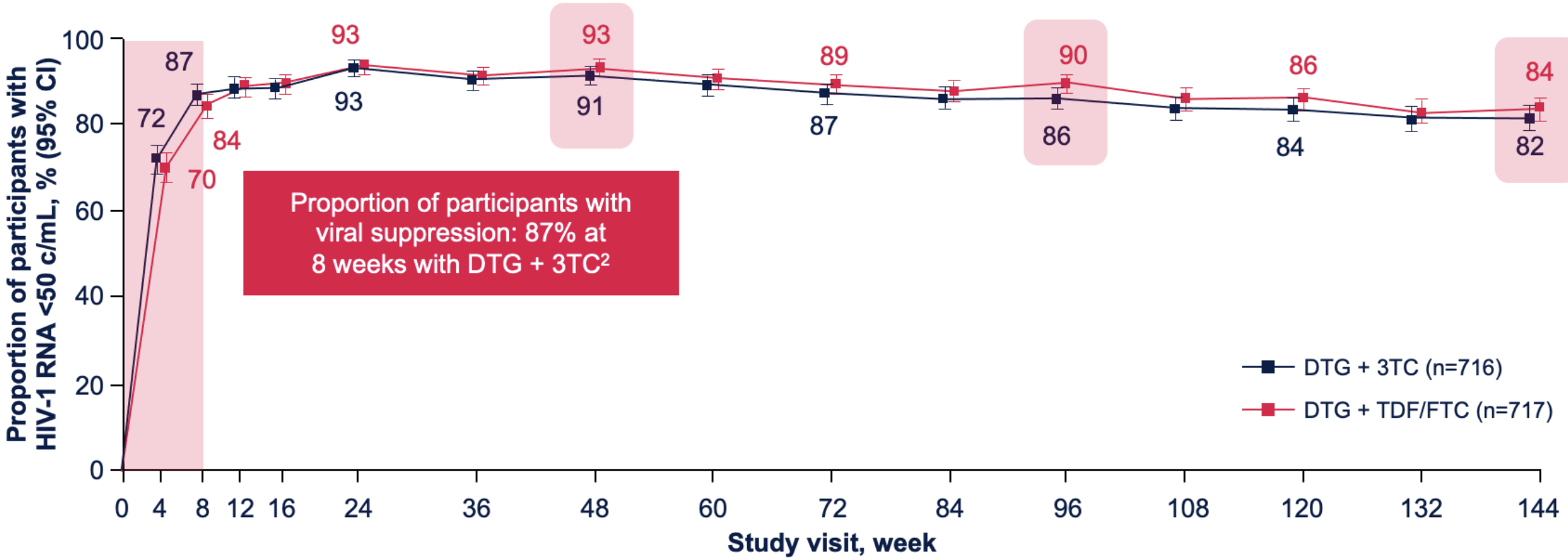
No emergent resistance to B/F/TAF has been observed through 2–5 years in Phase 3/4 trials of >3,500 participants

Study	Population	Comparator	B/F/TAF duration[a] (Years)	Resistance (n)[b]	
				B/F/TAF	Comparator
1489[1,2]	Naïve (314 vs 315; adults)	DTG/ABC/3TC	5 (includes 2yr open label)	0	2[c] (both M184V)
1490[1,2]	Naïve (320 vs 325; adults)	DTG+F/TAF	5 (includes 2yr open label)	0	0
1844[3]	Suppressed (282 vs 281; adults)	DTG/ABC/3TC	2 (includes 1yr open label)	0	0
1878[4]	Suppressed (290 vs 288; adults)	Boosted PI + 2 NRTIs	2 (includes 1yr open label)	0	1[d] (L74V)
1961[5]	Suppressed (234 vs 236; adults)	E/C/F/(TAF or TDF) ATV+RTV+F/TDF	2 (includes 1yr open label)	0	1[d] (M184M/I/V)
4449[6]	Suppressed (86; ≥ 65years old)	-	2	0	-
4030[7]	Suppressed (284 vs 281)	DTG + F/TAF	1	0	0
BRAAVE 2020[8]	Suppressed (328 vs 165; African Americans)	2 NRTIs + 3rd agent	1.5	0	0

[a] Comparator duration was 1 year except in ART-naïve studies which was 3 years. [b] Resistance testing performed for participants with confirmed viremia with second HIV-1 RNA ≥200 c/mL or ≥200 c/mL at last visit, with no re-suppression of HIV-1 RNA to <50 c/mL while on study drug. [c] Two DTG/ABC/3TC participants on blinded study drug of DTG/ABC/3TC developed M184V, switched to B/F/TAF and achieved HIV-1 RNA < 50 cp/mL at their next visit; [d] Study 1878: Participant on DRV+RTV+ABC/3TC developed ABC mutations L74V; Study 1961: Participant on E/C/F/TAF developed M184M/I/V
1. Walmsley S, et al. CROI 2021 [Abstract 494]. 2. Orkin C, et al. HIV Glasgow 2022 [Poster P088]. 3. Brar I, et al. IDWeek 2020 [Abstract 1028; poster presentation]. 4. Andreatta K, et al. EACS 2021 [Abstract P26]. 5. Kityo C, et al. IAS 2019 [Abstract MOAB0106] July 22, 2022. 6. Maggiolo F, et al. HIV Med 2022. doi: 10.1111/hiv.13319. 7. Sax P, et al. Clin Infect Dis 2021; 73:e485–e492. 8. Kumar P, et al. IAS 2021; [Poster 802].

DTG + 3TC Has Demonstrated Rapid and Durable Efficacy in Treatment-naïve Participants Through 144 Weeks

GEMINI-1 and -2[1,2]



A DTG-based 3DR did not deliver additional potency, speed or durability of antiviral efficacy versus DTG + 3TC

1. Cahn P, et al. AIDS 2022;36:39–48
2. Cahn P, et al. J Acquir Immune Defic Syndr 2020;83:310–8

OPEN

Three-year durable efficacy of dolutegravir plus lamivudine in antiretroviral therapy – naive adults with HIV-1 infection

Pedro Cahn[a], Juan Sierra Madero[b], José R. Arribas[c], Andrea Antinori[d], Roberto Ortiz[e], Amanda E. Clarke[f], Chien-Ching Hung[g], Jürgen K. Rockstroh[h], Pierre-Marie Girard[i], Jörg Sievers[j], Choy Y. Man[k], Rimgaile Urbaityte[l], Daisy J. Brandon[l], Mark Underwood[k], Keith A. Pappa[k], Lloyd Curtis[l], Kimberly Y. Smith[k], Martin Gartland[k], Michael Aboud[j], Jean van Wyk[j] and Brian Wynne[k]

Objective: To assess efficacy and safety of dolutegravir (DTG) + lamivudine (3TC) vs. DTG + tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in treatment-naive adults with HIV-1 in the prespecified 144-week secondary analyses of GEMINI-1 and GEMINI-2.

Design: Identical, multicenter, phase III, randomized, non-inferiority studies (double-blind through 96 weeks).

Methods: Participants with HIV-1 RNA ≤500 000 copies/ml and no major viral resistance mutations to nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, or protease inhibitors were randomized 1:1 to once-daily DTG + 3TC or DTG + TDF/FTC.

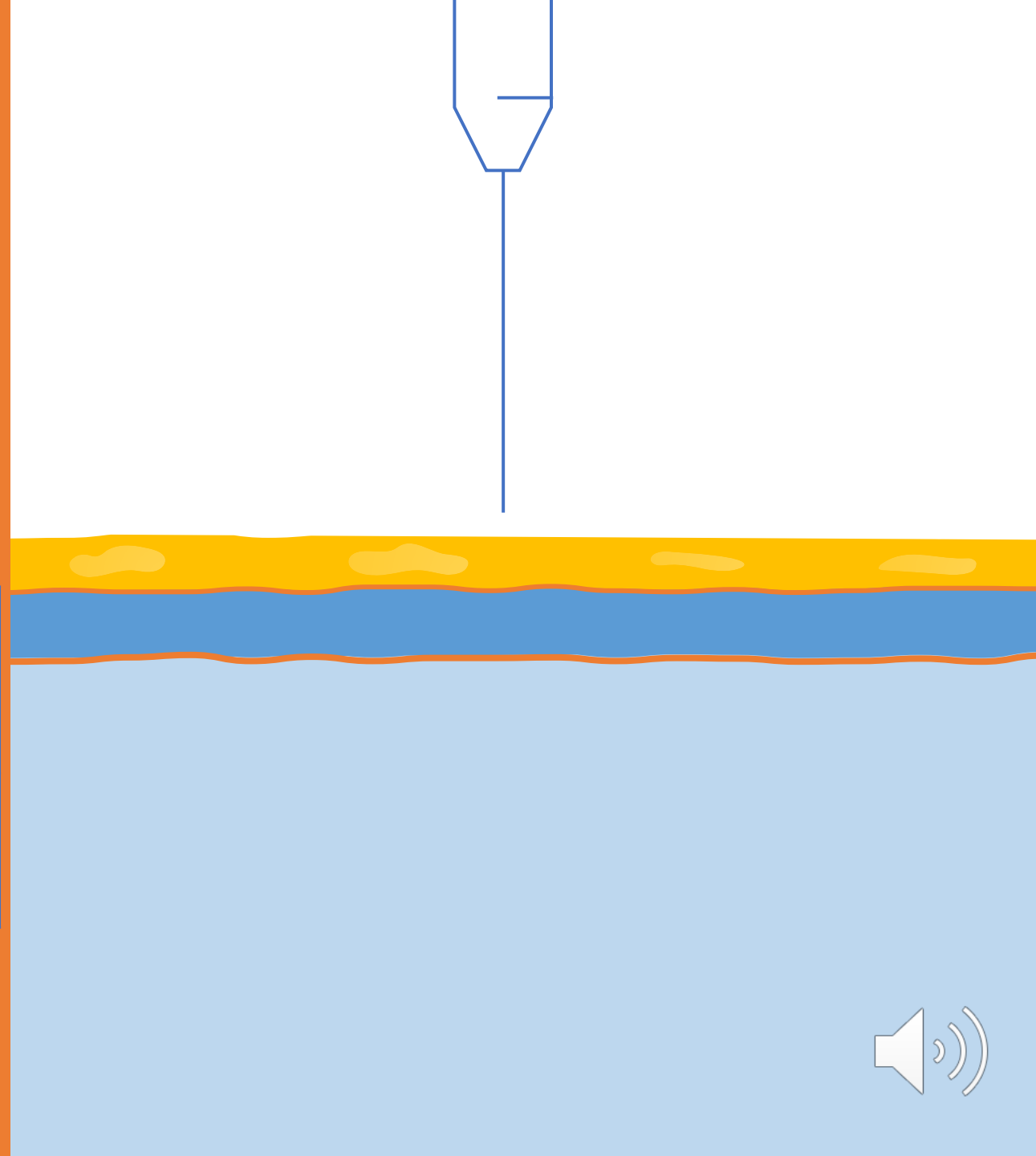
Results: At week 144, DTG + 3TC ($N = 716$) was noninferior to DTG + TDF/FTC ($N = 717$) in proportion of participants achieving HIV-1 RNA <50 copies/ml (Snapshot algorithm) in the pooled analysis (82% vs. 84%, respectively; adjusted treatment difference [95% confidence interval (CI)], −1.8% [−5.8, 2.1]), GEMINI-1 (−3.6% [−9.4, 2.1]), and GEMINI-2 (0.0% [−5.3, 5.3]). Twelve DTG + 3TC participants and nine DTG + TDF/FTC participants met protocol-defined confirmed virologic withdrawal (CVW) criteria; none developed treatment-emergent resistance. One DTG + 3TC participant who did not meet CVW criteria developed M184V at week 132 and R263R/K at week 144, conferring a 1.8-fold change in susceptibility to DTG; non-adherence to therapy was reported. Significantly fewer drug-related adverse events occurred with DTG + 3TC vs. DTG + TDF/FTC (20% vs. 27%; relative risk [95% CI], 0.76 [0.63–0.92]). Renal and bone biomarker changes favored DTG + 3TC.

Where are we NOW with long-acting ART?

CABOTEGRAVIR (CAB) + RILPIVIRINE (RPV)
LA every 2-MONTH OR 1-MONTH regimen*

6
treatments per year‡

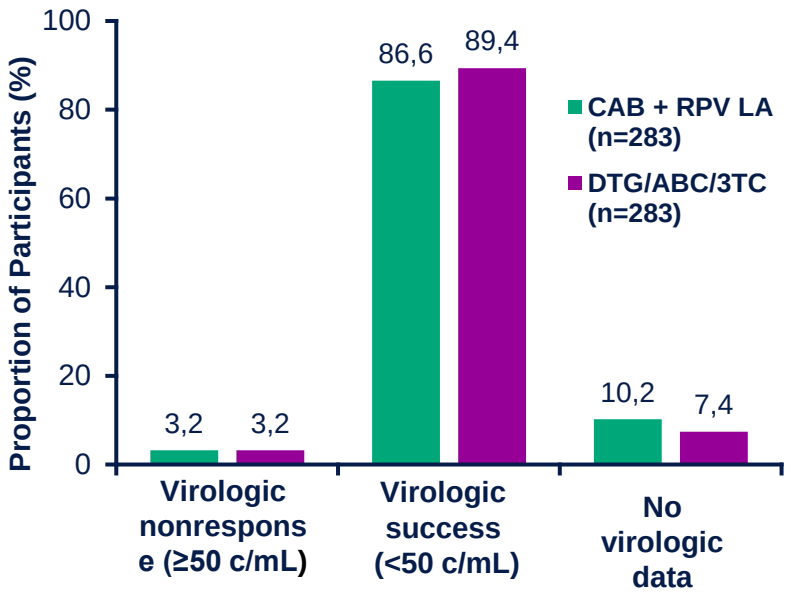
European Guidelines (Oct 2021)	US Guidelines (Feb 2022)	International AIDS Society (Oct 2020)
CAB + RPV LA Q8W	CAB + RPV LA Q8W and Q4W	CAB + RPV LA Q8W and Q4W



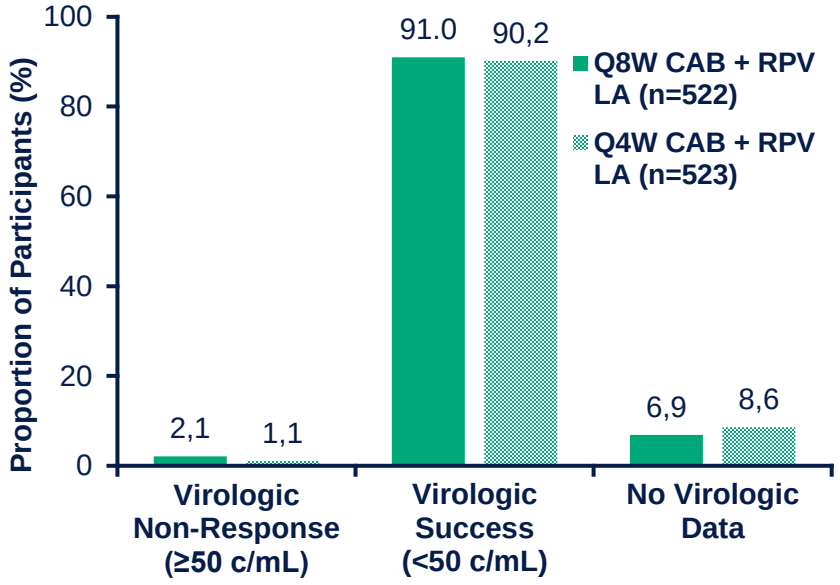
INJECTABLE 2DR in FIRST LINE & SWITCH

Virologic Snapshot outcomes at Week 96 (ITT-E)

FLAIR (naive) [1,2]



ATLAS-2M (switch) [3]



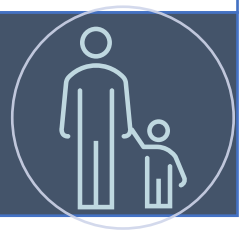
CAB+ RPV LA remains noninferior to DTG/ABC/3TC (<50 c/mL) at Week 96
CAB+RPV LA Q8W remains non inferior to Q4W (<50 c/mL) at Week 96

1.Orkin C, et al. CROI 2020. Poster 0482. Available at: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2020/1430_9_Orkin_00482.pdf (accessed December 2022). 2. Orkin C, et al. Lancet HIV. 2021;8(4):e185-e196. 3. Jaeger et al. CROI 2021; Virtual. Science Spotlight 1753. Available at: https://www.vcroi2021.org/sessions/19764919/subsession/25642355/WEEK-96-EFFICACY-AND-SAFETY-OF-CABOTEGRAVIR--RILPIVIRINE-EVERY-2-MONTHS-ATLAS-2M (accessed December 2022).

Not everyone can/will take oral treatment

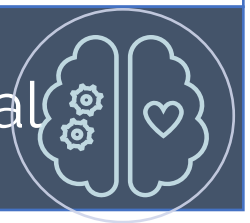
Biological

- Dysphagia
- Side events
- Drug interaction
- Malabsorption
- Cognitive problems



Psychological

- Pill fatigue
- Anxiety
- Depression
- HIV constant reminder

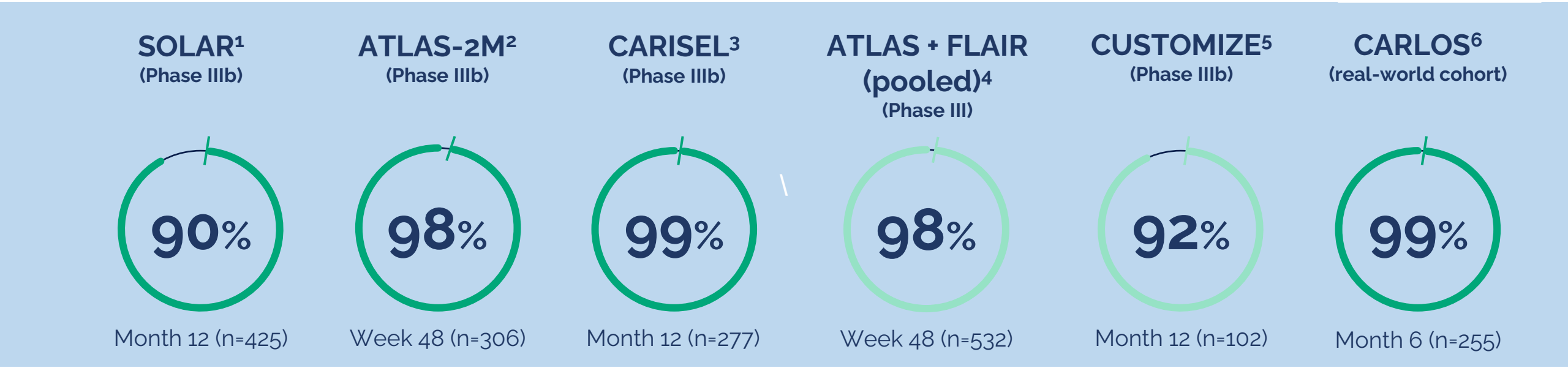


Social

- Inadvertent disclosure
- Convenience

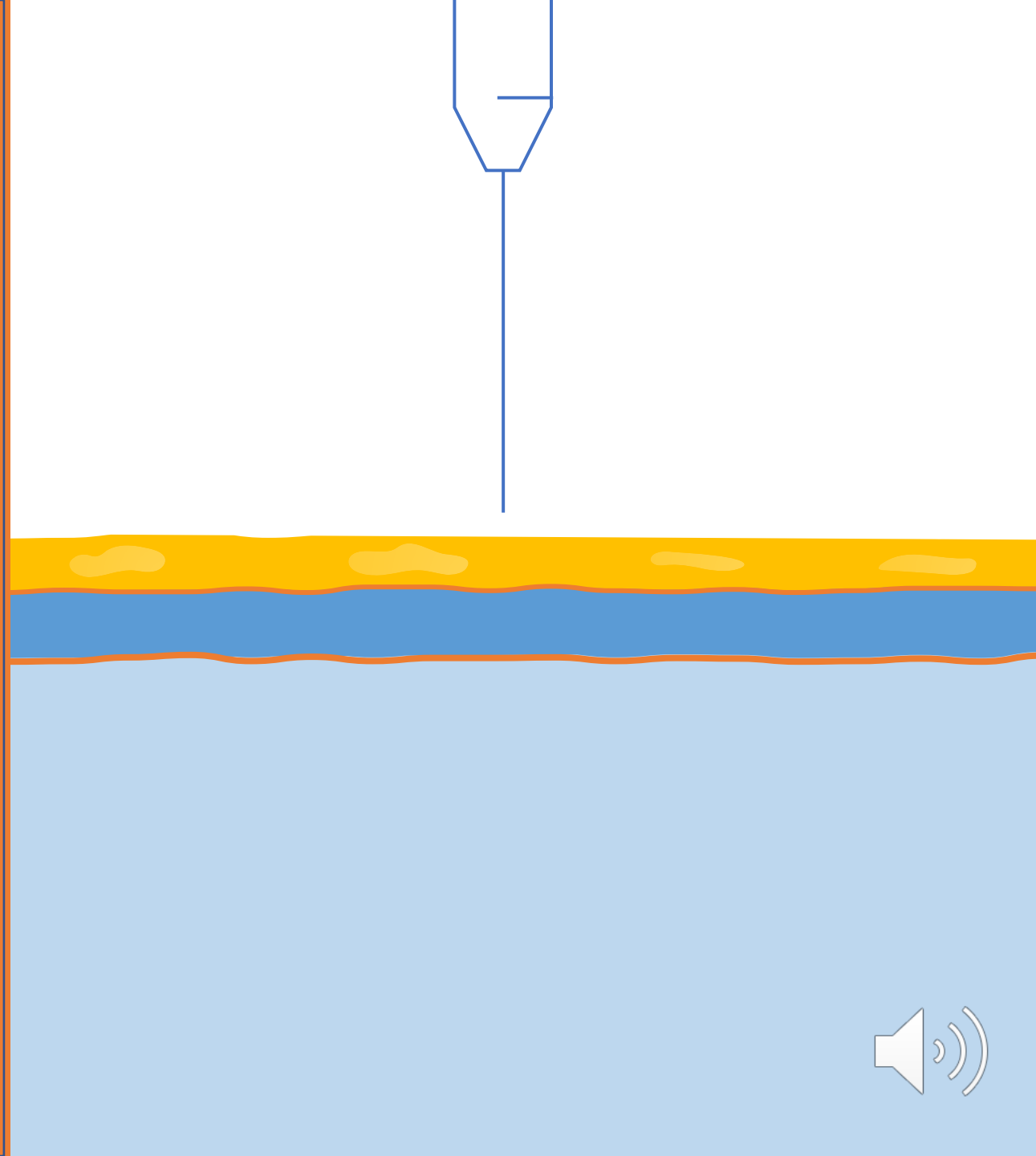
Injectable therapy was preferred vs daily oral therapy

Phase III and Real-world Cohorts:



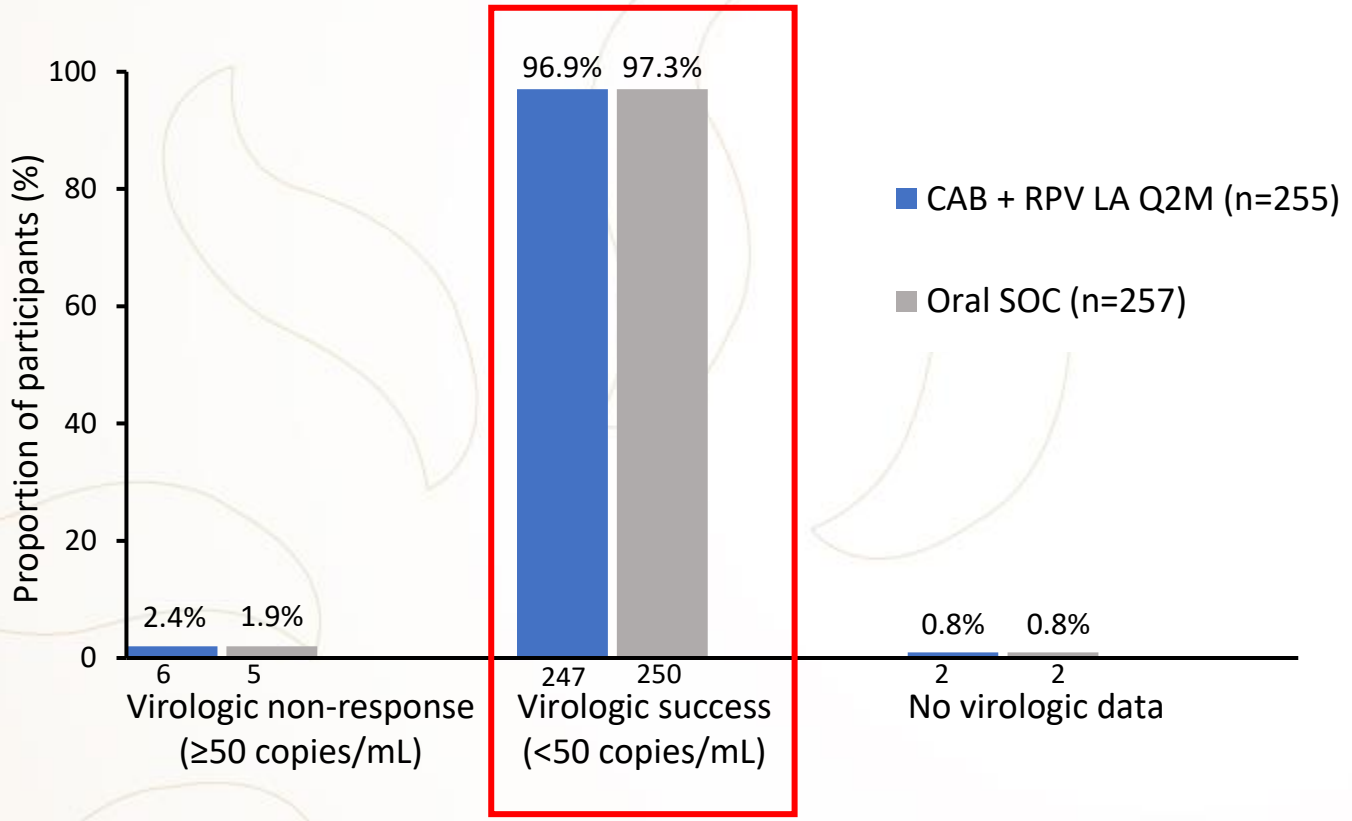
1. Ramgopal MN, et al. Lancet HIV 2023;10(9):e566–577 (and suppl. appendix)
2. Chounta V, et al. Patient 2021;14:849–62 **3.** Lutz T, et al. HIV Glasgow 2022. Poster P123
4. Murray M, et al. AIDS Behav 2020;24:3533–44
5. Garris CP, et al. J Int AIDS Soc 2022;25:e26006; **6.** Scherzer J, et al. IAS 2023. Poster EPE0863

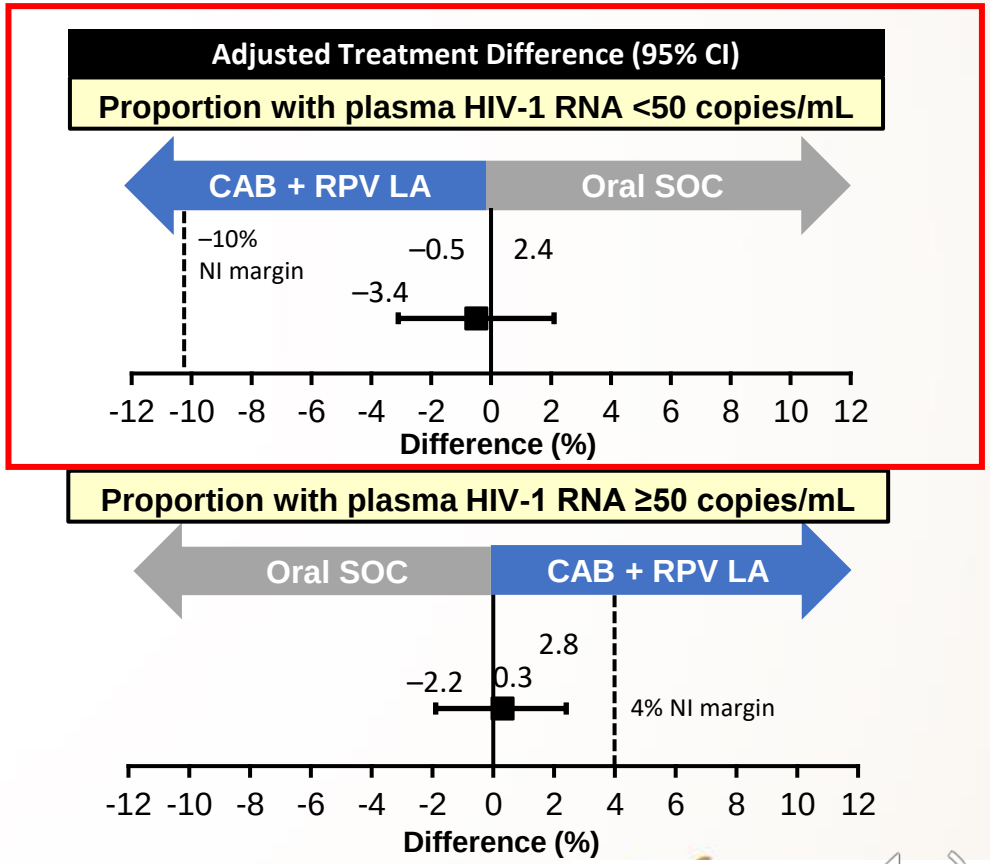
Implementation



INJECTABLE 2DR in SWITCH in AFRICA

Randomized trial of Cabotegravir and Rilpivirine Long-acting in Africa (CARES):Week 48 Results





Kityo et al. CRC 2024

ACTG A5359 LATITUDE: Study Design

Prospective, randomized, open-label, phase III trial

People living with HIV with poor viral response after ≥6 mo ART or loss to f/u with ≥6 mo non-adherence, no HBV, no INSTI or RPV RAM historically or by screening (N = 434)

Step 1: Up to 24 Wk

SOC Oral ART + Conditional economic incentives

Eligible for randomization to Step 2 with HIV-1 RNA <200 c/mL starting at Wk 4 (originally after Wk 24)

Step 2: 52 Wk

LA CAB + RPV Q4W (n = 146)

SOC Oral ART (n = 148)

Step 3: 52 Wk

LA CAB + RPV Q4W

Step 4 (Observational Phase): Participants who received ≥1 dose of LA CAB + RPV and are no longer eligible for injections switch to receiving 52 wk of oral ART

- **Primary endpoint:** treatment regimen failure defined as earliest confirmed virologic failure or discontinuation during step 2
- **Key secondary endpoints:** virologic failure, treatment-related failure, permanent treatment discontinuation

Rana. CROI 2024. Abstr 212.

ACTG A5359 LATITUDE: Efficacy Outcomes

DSMB stopped study prematurely

Primary Outcome			Secondary Outcomes								
Regimen Failure	28	47	Virologic Failure	6	28	Treatment-related Failure	9	29	Permanent TRT-DISC	25	30
VF	5	28				VF	6	28			
TRT-DISC	23	19				TRT-DISC (AE)	3	1			

Rana. CROI 2024. Abstr 212.

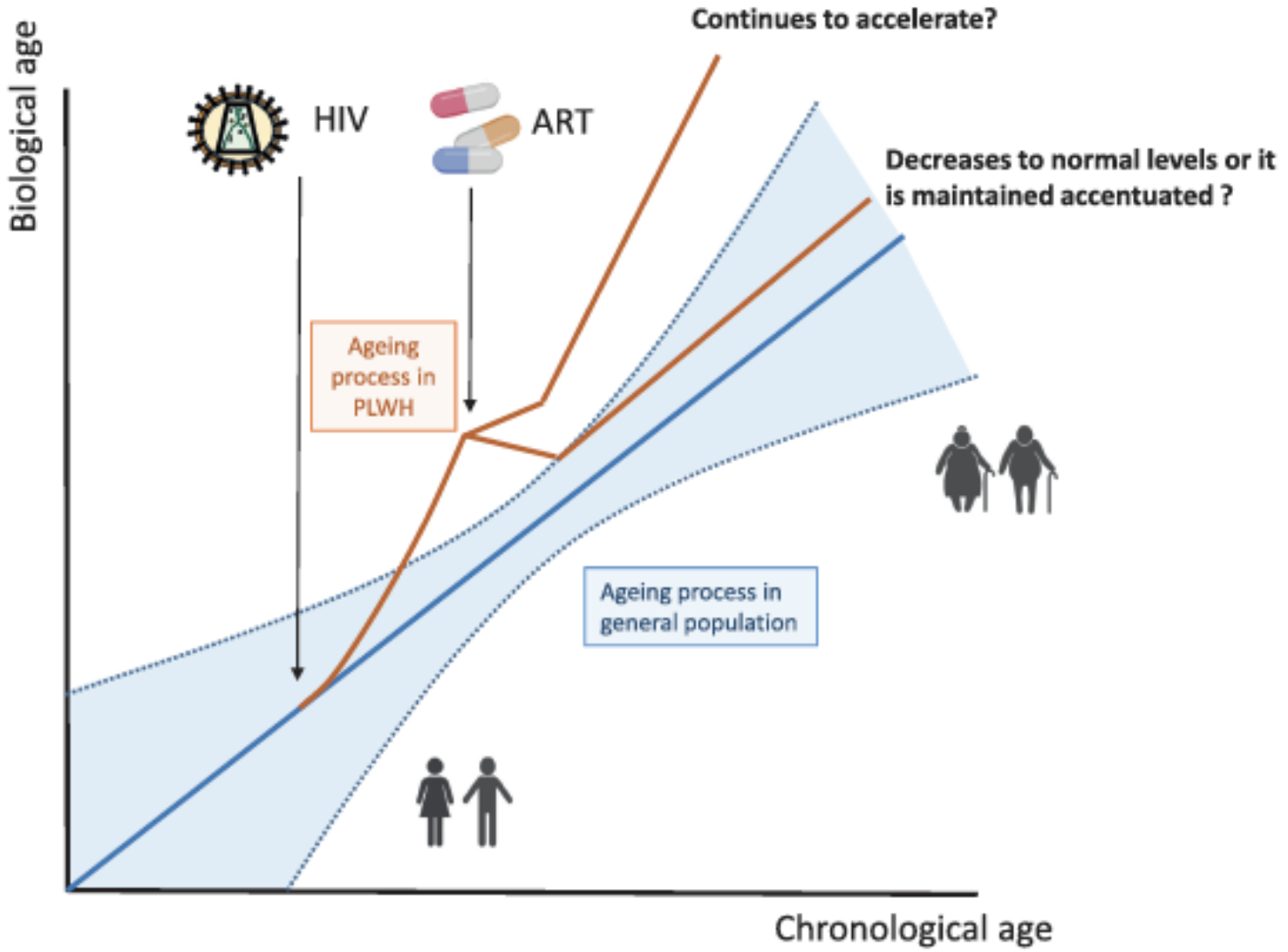
HIV: do we really need new drugs?

- YES…… therapy has to be taken for life

- YES……new drugs with new mechanism of action and with less toxicities are needed

AGING AND HIV

Thanks to effective **HIV treatment**, the number of **older adults** living with HIV is **increasing**.



www.thelancet.com Vol 77 Month March, 2022

Clinical Infectious Diseases
MAJOR ARTICLE

Time Trends in Causes of Death in People With Human Immunodeficiency Virus: Insights From the Swiss HIV Cohort Study

M. S. R. Weber,[1,2] J. J. Duran Ramirez,[1,2] M. Hentzien,[3,4,5] M. Cavassini,[6] E. Bernasconi,[7] E. Hofmann,[8] H. Furrer,[8] H. Kovari,[9] M. Stöckle,[10] P. Schmid,[11] D. Haerry,[12] D. L. Braun,[1,2,a] H. F. Günthard,[1,2,a] K. Kusejko[1,2,a]; and the Swiss HIV Cohort Study[b]

Non-AIDS cancers now the leading cause of death
AIDS and liver complications have dropped dramatically

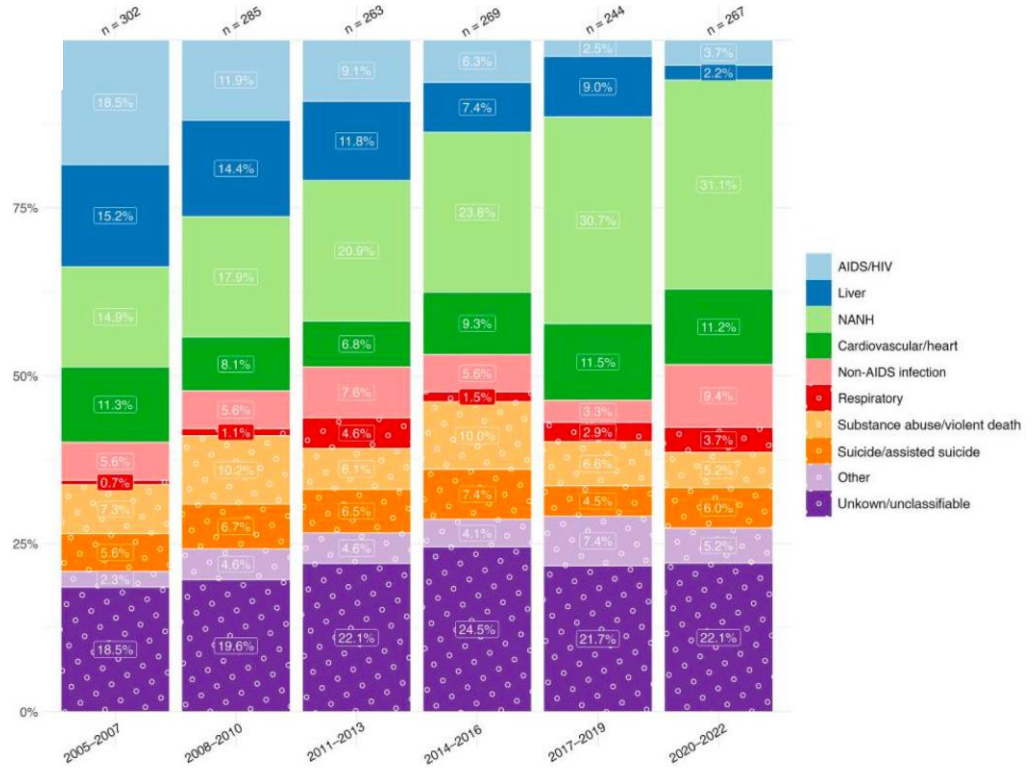
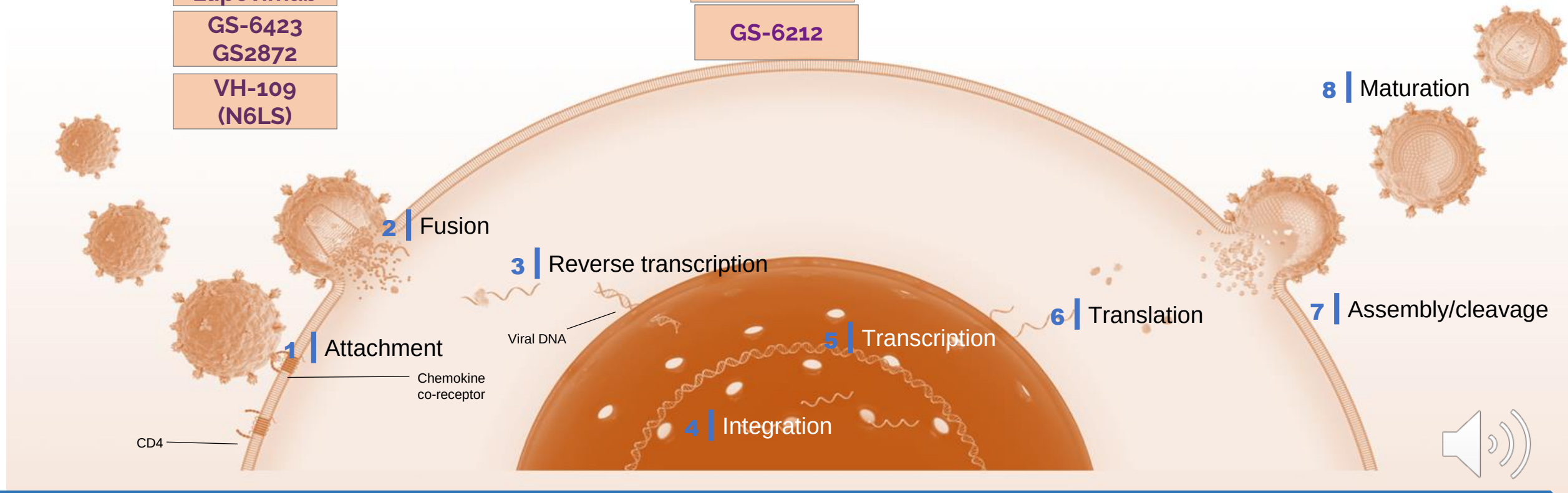


Figure 1 Time trends in causes of death from 2005 to 2022, stratified by 3-year periods. Single causes of death are categorized into broader categories as outlined in Table 1. The x-axis includes time periods from 2005 to 2022, grouped into 3-year intervals; y-axis, the percentage distribution for each cause-of-death cate y; numbe above bar, the total reported deaths for the corresponding 3-year period. Abbreviations: HIV, human immunodeficiency virus; NANH, non-AIDS, non-hep

? FUTURE

Compounds in clinical development for treatment

Entry inhibitor	bNAb	NRTTI	NNRTI	Integrase inhibitor	Protease inhibitor	Capsid inhibitor	Maturation inhibitor
Albuvirtide	UB-421	Islatravir	Elsulfavirine	CAB-ULA	GS-1156	Lenacapavir	GSK937
	VRC 01/LS VRC 07/LS	MK 8527	GS-5894	VH-184		VH-280 VH-499 r	
	PG121 + Elipovimab			GS-1720			
	GS-6423 GS2872			GS-6212			
	VH-109 (N6LS)						



H I V L I F E C Y C L E

LEN Future Pipeline

HIV treatment							
Oral LEN				**Injectable LEN**			
Dosing	**Foundation**		**Partner**	**Dosing**	**Foundation**		**Partner**
QD		+	**Bictegravir** Phase 2/3	**Q3M**		+	**INSTI Injectable** Phase 1
QW		+	GS-1720 **INSTI Oral** Phase 1			+	**NRTI** Preclinical
		+	GS-5894 **NNRTI** Phase 1	**Q6M**		+	**Teropavimab + Zinlirvimab** Phase 2
		+	**Islatravir (Merck)** Phase 2				

GS-6212

Oral LEN Injectable LEN

LEN is being developed as the foundation for future long-acting oral and injectable therapies addressing individual needs and preferences

HIV Broadly Neutralizing Antibodies (bNAbs)

Features

- Human monoclonal antibodies able to neutralize wide range of HIV-1 isolates
- Target HIV-1 envelope
- Enhance various effector functions
- Can be genetically engineered to combine multiple specificities or extend half-life

Potential Clinical Uses

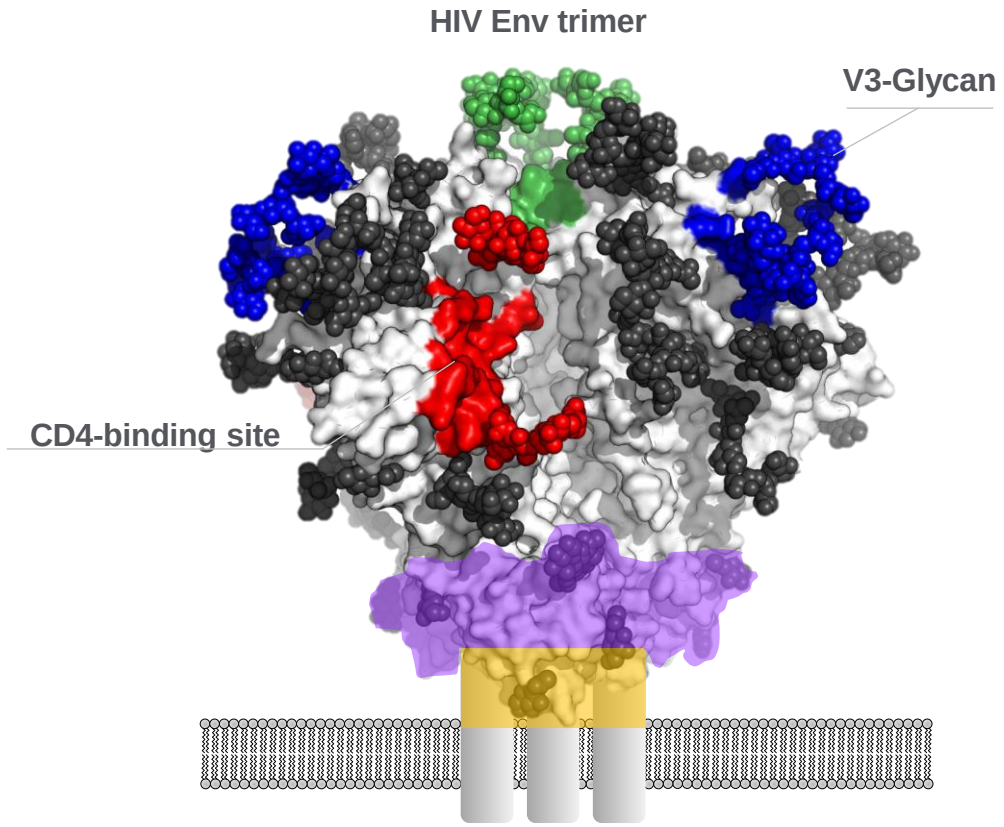
- HIV treatment intensification by concomitant use of ART + bNAbs
- Maintenance therapy in virologically suppressed individuals
- HIV immunotherapy: possible treatment alternative (eg, MDR or ART intolerance)
- Prevention: pre- and postexposure prophylaxis; PMTCT (for late presenters)

Potential Advantages

- Infrequent dosing
- No cross-resistance with ARVs
- Established paradigms for therapeutic use in other disease areas
- Potential for overcoming adherence challenges and for less stigma
- Potential to enhance HIV-specific immunity

bNAbs Teropavimab and Zinlirvimab

- Teropavimab (TAB; GS-5423; 3BNC117-LS) and zinlirvimab (ZAB; GS-2872; 10-1074-LS) are broadly neutralizing antibodies (bNAbs) against the CD4-binding site of gp120 and a non-overlapping epitope on the V3 glycan of HIV-1 Env, respectively.
- Both antibodies were modified to extend their half-lives for long-acting therapy that may allow for dosing every 6 months.
- An estimated > 50% of clade B viruses are highly susceptible to both bNAbs and > 90% are highly susceptible to either bNAb with a 90% inhibitory concentration (IC_{90}) < 2 µg/mL.



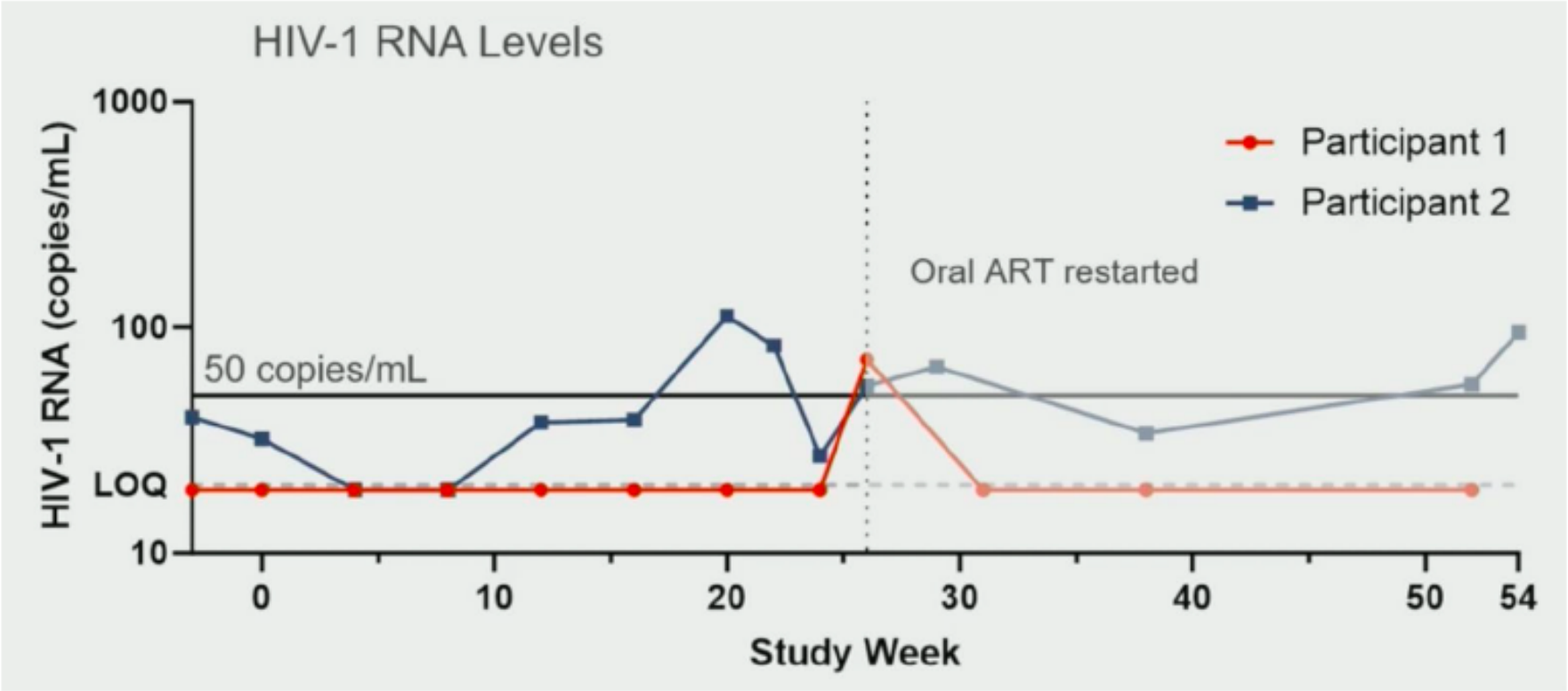
- **We hypothesize that combining TAB and ZAB with a long-acting antiviral agent could provide a complete long-acting therapeutic regimen for HIV treatment.**

Yoon H, et al. CATNAP: a tool to compile, analyze and tally neutralizing antibody panels. *Nucleic Acid Res.* 2015 Jul 1;43(W1):W213-9. PMID 26044712.

LEN/TAB/ZAB in those for whom only one antibody was fully active (IC90 < 2 ug/mL; n=10)

CROI 2024 Conference on Retroviruses and Opportunistic Infections March 3-6 | Denver, Colorado

Lenacapavir Plus bNAbs for People With HIV and Sensitivity to Either Teropavimab or Zinlirvimab
Joseph J. Eron[1], Paul P. Cook[2], Megha Mehrotra[3], Hailin Huang[3], Marina Caskey[4], Gordon Crofoot[5], Edwin DeJesus[6], Linda Gorgos[7], Laurie VanderVeen[3], Olayemi O. Osiyemi[8], Cynthia Brinson[9], Sean E. Collins[3]



- At week 26, 8/10 maintained suppression
- Persistent low-level viremia seems common

Role of bNAbs in HIV therapy

- Ultra-long-acting injectables (6 months+) for treatment are highly desired options
- When used in combination, they are effective and safe
  - Potency seems lower than standard ART, perhaps due to pre-existing resistance
  - Low-level viremia common?
- People with MDR HIV seem to retain susceptibility to bNAbs
  - Combination of very long-acting bNAbs with small molecules (lenacapavir) is a promising alternative for those with MDR
- Screening for resistance to bANbs will be needed, and will be a major limitation for implementation

Agenda

Where we are

Where we are going to

- ✓HIV epidemiology
- ✓HIV prevention
- ✓HIV therapy
- ✓HIV cure

is rare

HIV Cure is Rare: Elimination and Durable ART-Free Suppression

2009 — **TIMOTHY RAY BROWN**

THE BERLIN PATIENT

2010 — **VISCONTI/SPARTAC/CHAMP**

POST TREATMENT CONTROL

2019 — **ADAM CASTILLEJO**

THE LONDON PATIENT

2020 — **LOREEN WILLENBERG**

THE SAN FRANCISCO PATIENT.

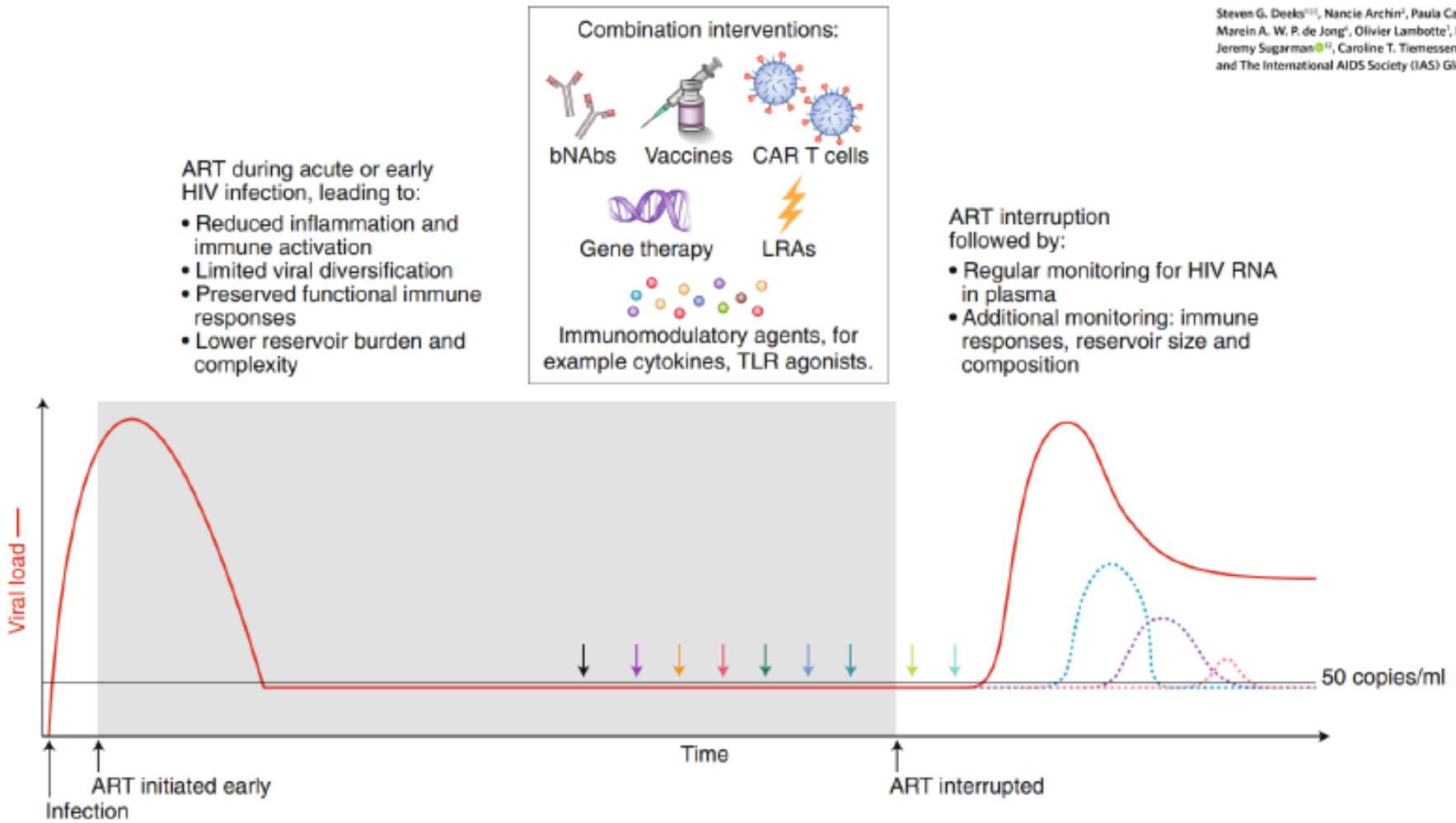
Hutter et al., N Engl J Med 2010; Gupta et al., Nature 2019; Gupta et al, Lancet HIV 2019; Jiang et al., Nature 2020

Immunotherapy: Multiple approaches are being pursued in the clinic

nature medicine REVIEW ARTICLE

Research priorities for an HIV cure: International AIDS Society Global Scientific Strategy 2021

Steven G. Deeks[1,22], Nancie Archin[2], Paula Cannon[3], Simon Collins[4], R. Brad Jones[5], Marein A. W. P. de Jong[6], Olivier Lambotte[7], Rosanne Lamplough[8], Thumbi Ndung'u[9,10,11], Jeremy Sugarman[12], Caroline T. Tiemessen[13], Linos Vandekerckhove[14], Sharon R. Lewin[15,16,17,22] and The International AIDS Society (IAS) Global Scientific Strategy working group*

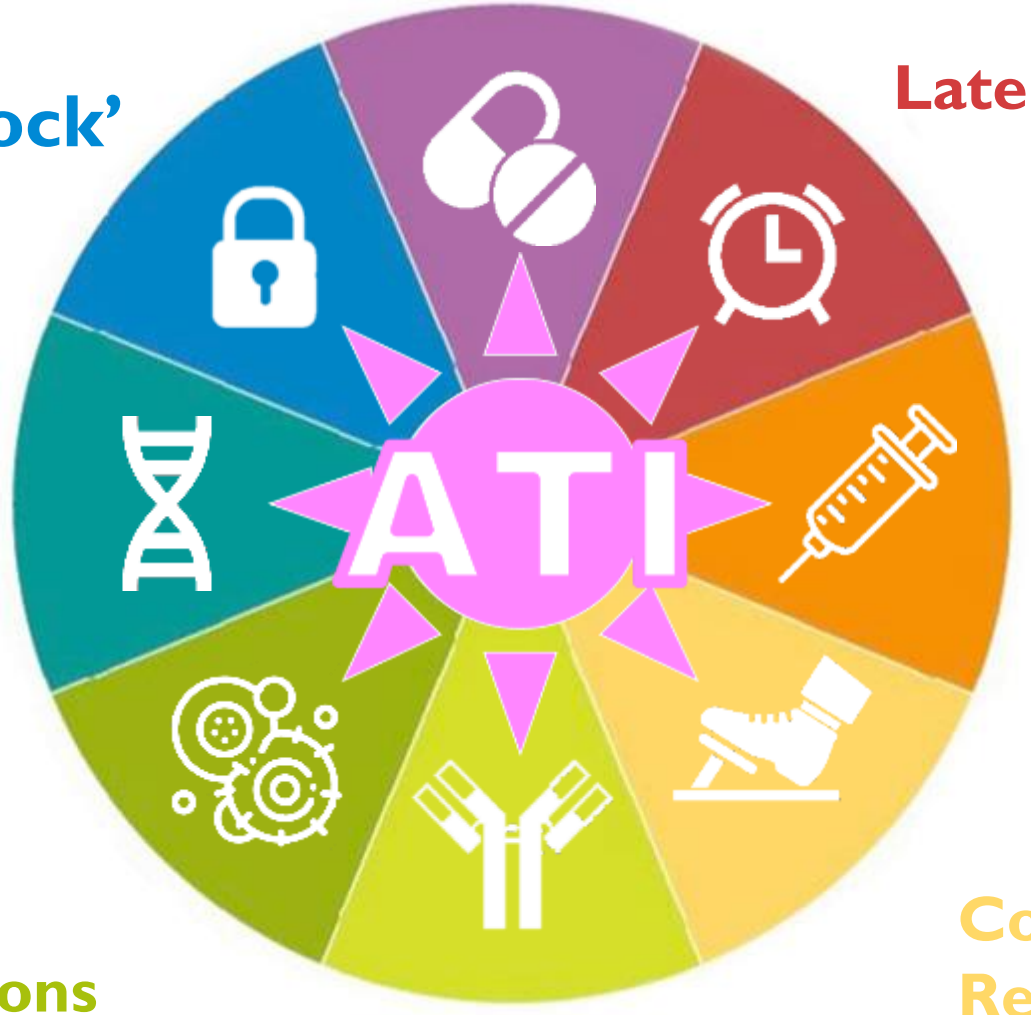


Most studies in people focused on T-cell based therapeutic vaccines, immune-modifying drugs, and neutralizing antibodies

Early Antiretroviral Treatment

‘Block and Lock’

Latency Reversal Agents



Cell & Gene Therapy

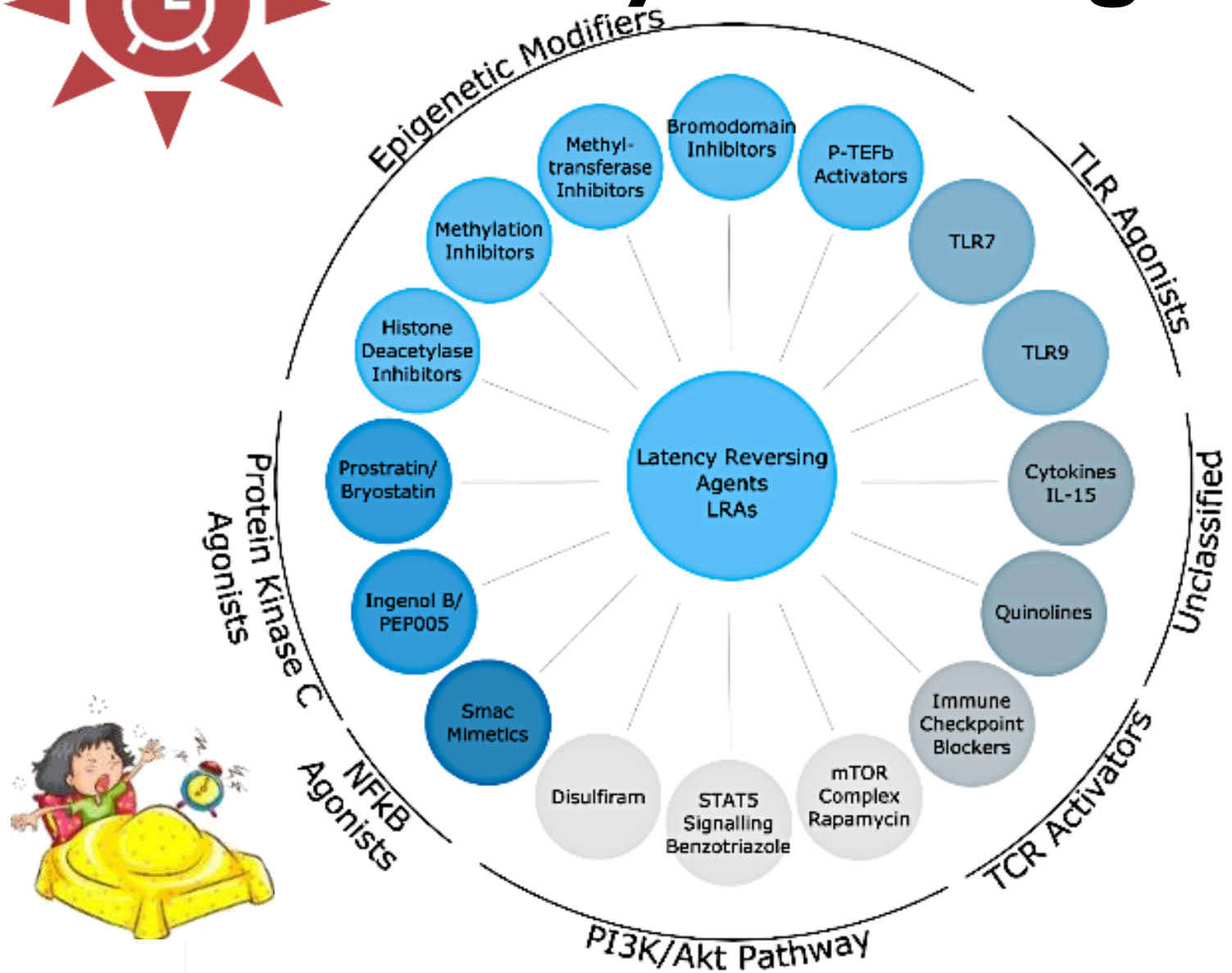
Immunotherapy Strategies

Stem Cell Transplantations

Co-Inhibitory Receptors

Broadly Neutralizing Antibodies

Latency-Reversing Agents



None are HIV specific

None are as potent as T-cell activation

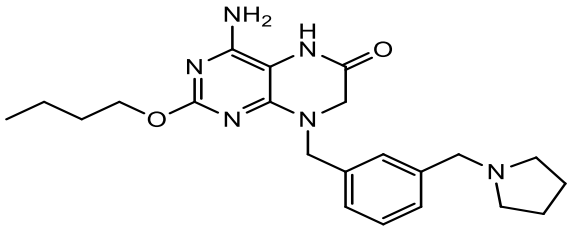
Unclear if virus is coming from all cells or just a few

Still need better latency-reversing agents

Kim, Anderson and Lewin. *Cell Host & Microbe* 2018

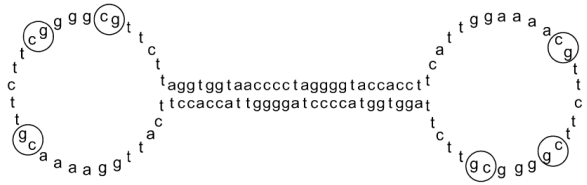
Lewin SR. Why Should We 'Shock and Kill'. Community Cure Workshop. Saturday July 21, 2018.

TLR7 & TLR9 Agonists



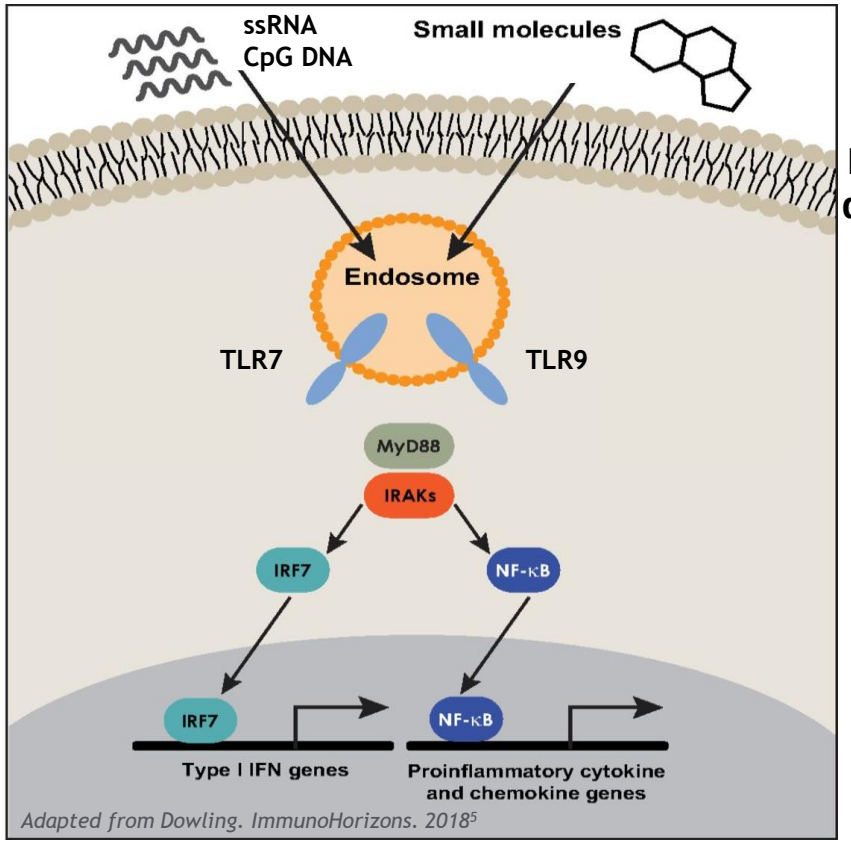
Vesatolimod[1] (GS-9620)

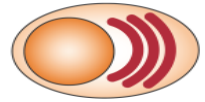
- **Orally bioavailable TLR7 agonist**
- **32-fold selectivity for TLR7 vs. TLR8 assessed by EC_{50}**



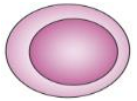
Lefitolimod[2] (GS-1703)

- **Selective TLR9 CpG-DNA agonist, subcutaneous injection**
- **Increased potency vs. other members of CpG-DNA class**





Plasmacytoid dendritic cells



B cells

TLR7 and TLR9 agonists stimulate immunity through plasmacytoid dendritic cell production of type I IFNs and cytokines[3,4]

Antiviral Cytokines: **IFNα/β, ISGs**

Acute Phase Cytokines: **IL-1, IL-1RA, IL-6, ITAC**

Activates CD4+ T-cells

Activates CD8+ T-cells, NKs, monocytes, APCs

APC, antigen presenting cells; CpG-DNA, cytosine-phosphate-guanosine deoxyribonucleic acid; EC_{50}: effective concentration 50%; IFN, interferon; IL, interleukin; ISG, interferon stimulating genes, ITAC, inducible t-cell chemoattractant; NK, natural killer cells; TLR, toll-like receptor.

1. Patinote C, et al. Eur J Med Chem. 2020 May 1; 193: 112238.
2. Wittig B, et al. Crit Rev Oncol Hematol. 2015 Apr;94(1):31-44.
3. Tsai A, et al. J Virol 2017;91(8):e02166-16.
4. Ram R, et al. CROI 2019. Seattle, WA. Poster 370.
5. Dowling DJ et al. ImmunoHorizons 2018, 2 (6) 185-197.

What is Cell and Gene Modification?

- A branch of **Regenerative Medicine**, an emerging field that involves the "process of replacing, engineering or regenerating human cells, tissues or organs to restore or establish normal function".

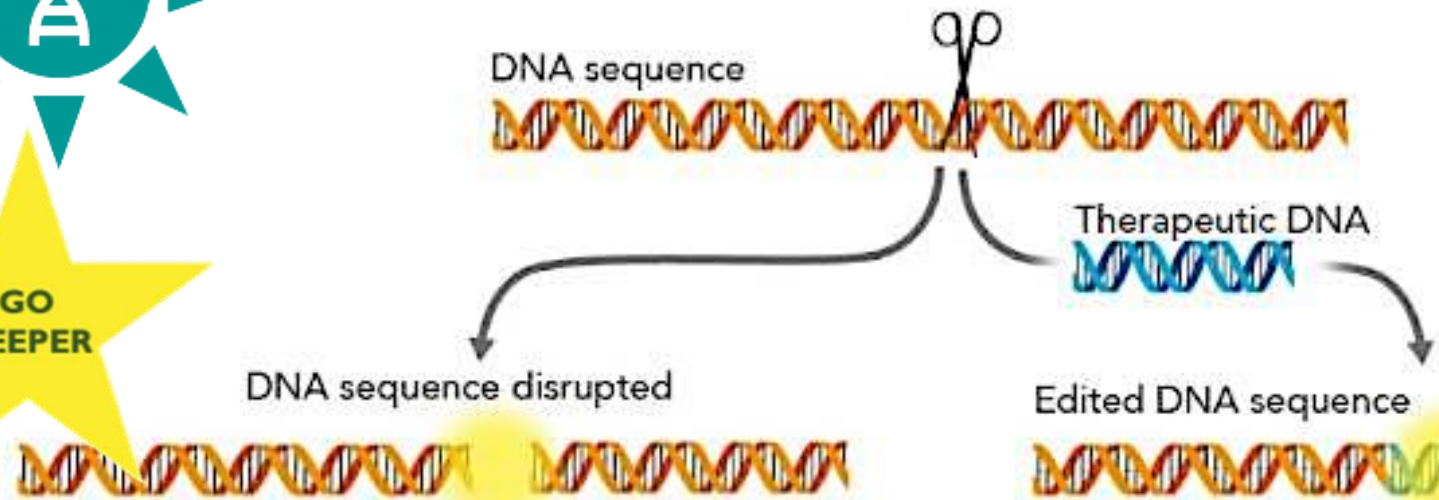
- **Gene therapy** is the delivery of therapeutic gene into a patient's cells to treat disease.

- **Cell therapy** is the delivery of intact, living cells into a patient to treat disease.

- Combination **Cell/Gene Modification** approaches that seek to insert genes into a patients' own cells to control or kill HIV are in clinical trials now.

GO DEEPER

Gene modification strategies



Gene editing for HIV Cure: example of site-specific platforms

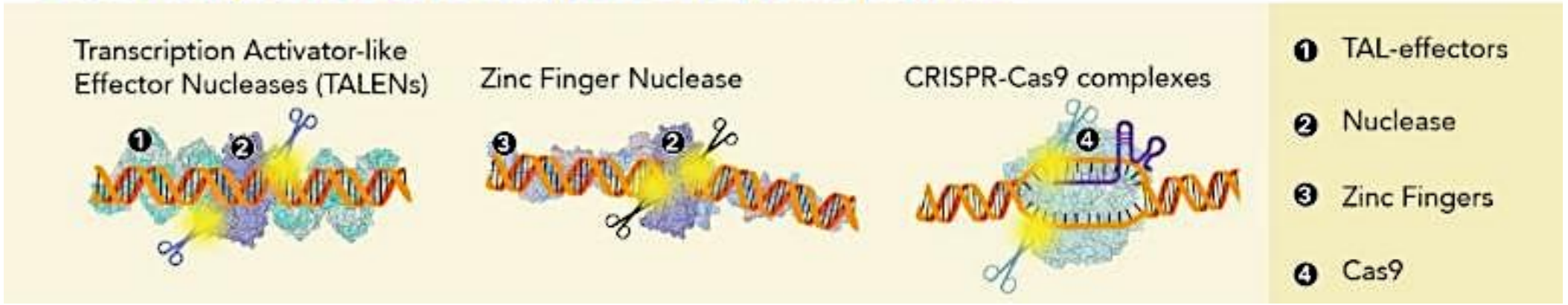
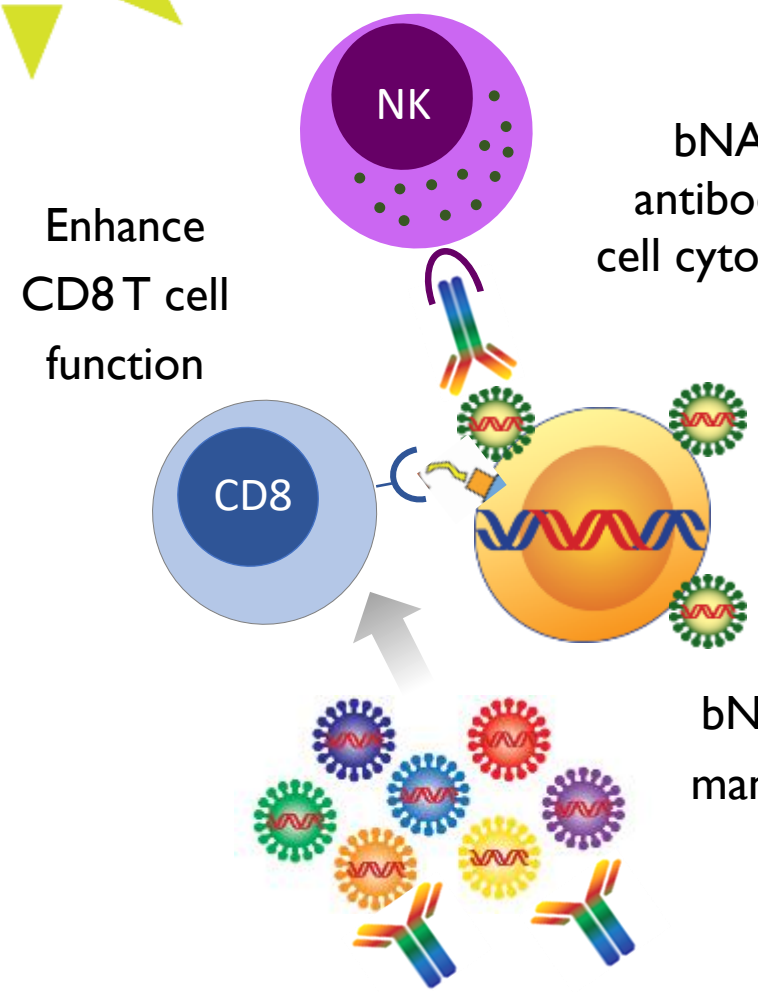


Illustration Credit: Grace Hsu, MS, CMI, Scientific Animation, Animation Lab: https://animationlab.utah.edu/

Broadly Neutralizing Antibodies (bNAbs)



Enhance CD8 T cell function

bNAbs facilitate antibody-dependent cell cytotoxicty (ADCC)

bNAbs can bind many HIV strains

Main obstacle

- Pre-existing resistance

Strategies

- Broad and potent
- Multiple
- Tri-specific
- Long-acting
- Novel delivery platforms
- Early administration
- Combine with other agents

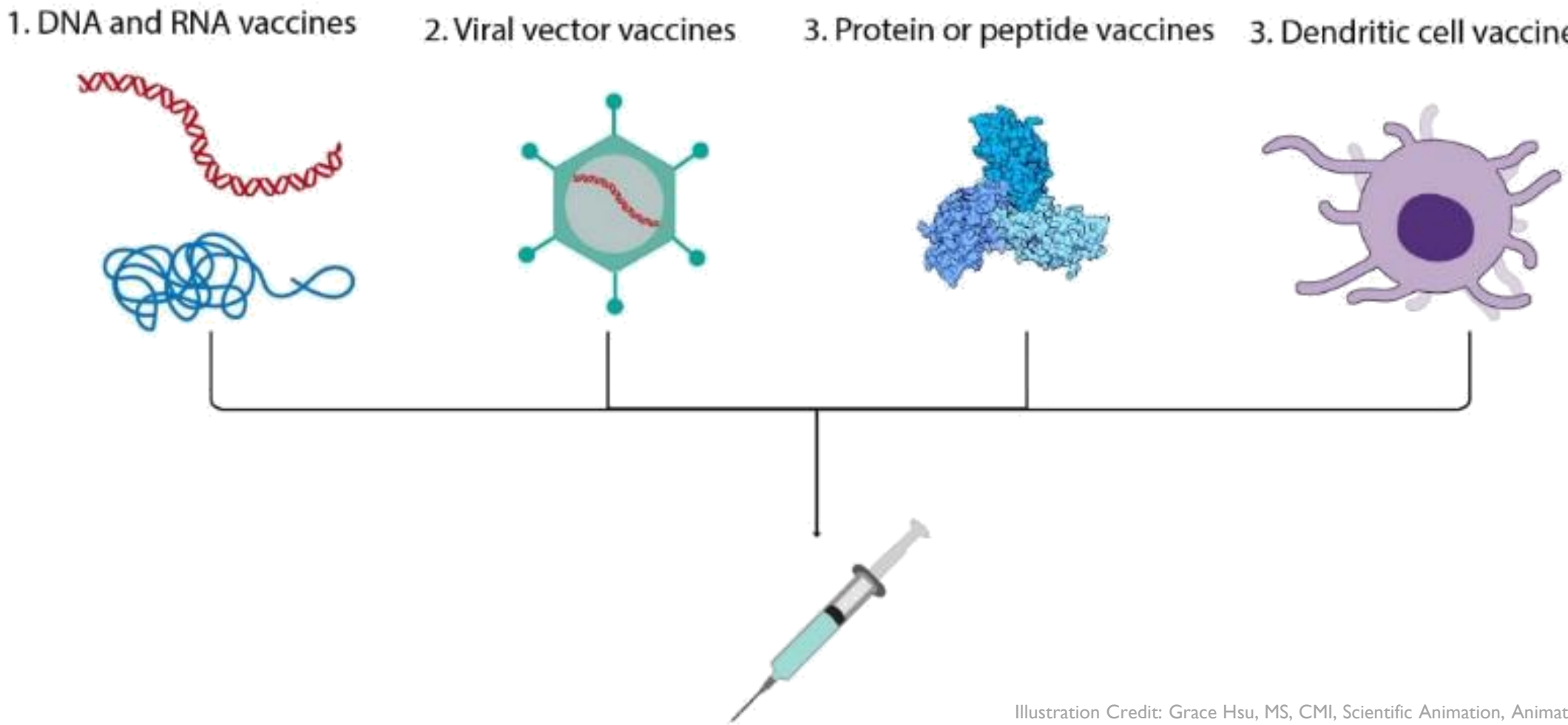
Kong, J Virol 2015; Barr, NEJM 2016; Scheid, Nature 2016; Caskey, Nature Med 2017; Hessell, Nature Med 2016; Liu, Science 2016; Nishimura, Nature 2017; Pardi, Nature Communications 2017; Gardner, Nature 2015; Pitman, Lancet 2018

bNAbs for HIV prevention, treatment or cure research

Compound / Company	Target	Notes	Status
ibalizumab	gp120	Already approved in the US and EU for treatment of MDR HIV.	Approved.
leronlimab (PRO 140) CytoDyn	CCR5	Once-weekly sub-cutaneous injection being studied in addition to ART for multi-drug resistance and as monotherapy maintenance therapy (without ART). Phase 3.	Phase 3.
UB-421 United BioPharma	CD4 binding	Infusion dosed either weekly or every two weeks as alternative to ART during treatment interruption. Phase 3.	Phase 3.
VRC01 and VRC01LS US NIH	CD4 binding	Intravenous infusion being studied in cure research and as PrEP (2 large phase 3 studies are ongoing). Sub-cutaneous dosing of infants to prevent transmission at birth or from breastfeeding. VRC01LS is a longer acting formulation. Results as PrEP expected late 2020.	Phase 3.
VRC07, VR07-523LS	CD4 binding	Engineered from VRC01. Being studied with cabotegravir-LA in ACTG trial.	Phase 2.
PGT-121 and GS-9722 (elipovimab). Gilead.	C3/V3	PGT121 is an IgG1 mAb that targets the V3 Env epitope. GS-9722 (elipovimab) is engineered from PGT-121.	Phase 1.
3BNC117 and 10-1074; Rockefeller University and Gilead	CD4 binding and C3/V3	Both bNAbs are available as LS long-acting formulations. Gilead Sciences signed for exclusive global development rights.	Phase 2.
N6 US NIH and ViiV	gp120	Developed by US NIH and now licenced to ViiV.	Phase 1.
Other mAbs: 10E8, trispecific bNAbs, PGDM1400	MPER, V2 and others	Mulitple compounds in preclinical and phase 1 studies.	Phase 1.

http://www.i-Base.info/hiv-pipeline-report-2020

Types of HIV Therapeutic Vaccines



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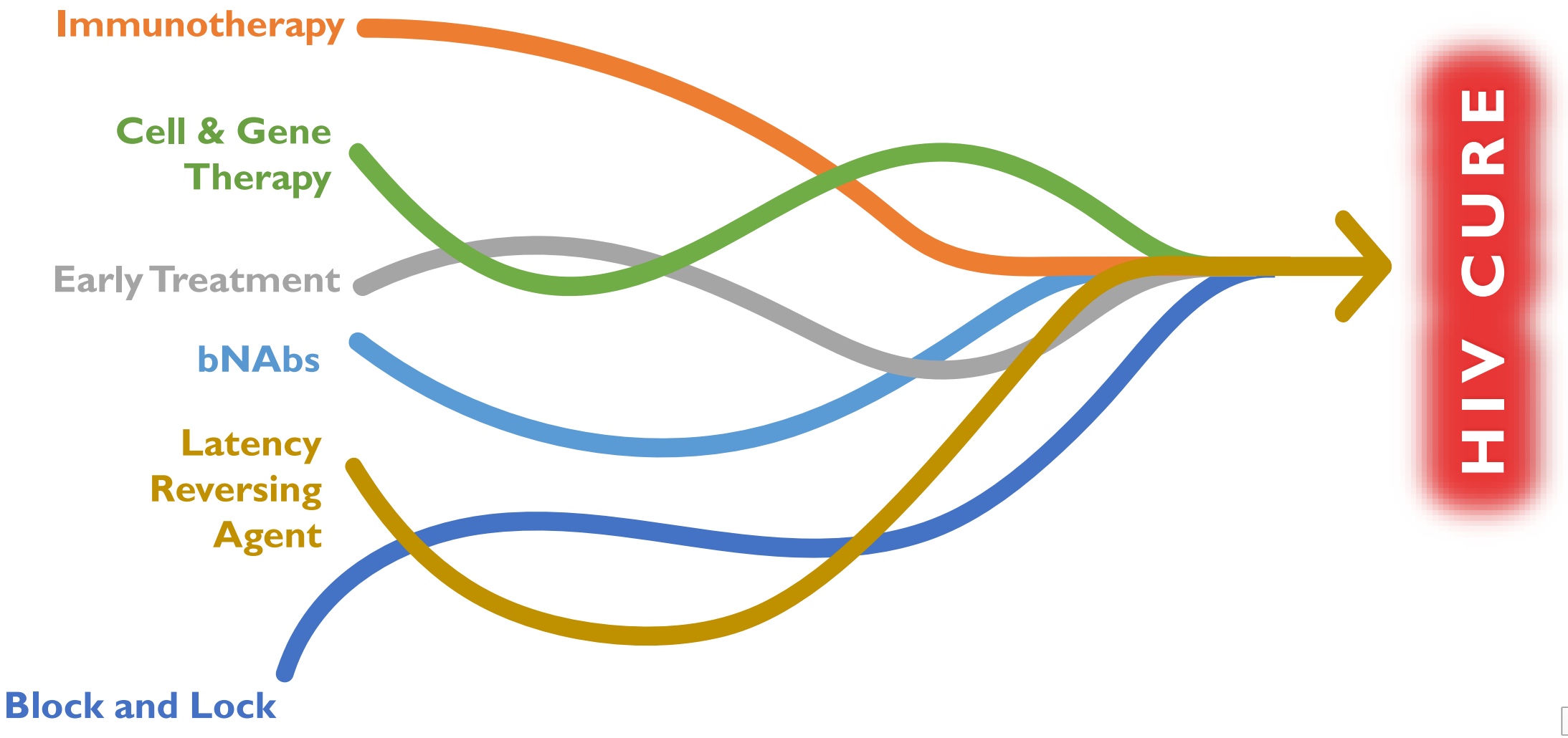
Combination Approaches



Grazie per l'attenzione