

Innovazione in HIV. Cosa significa?

Le innovazioni del Long- acting

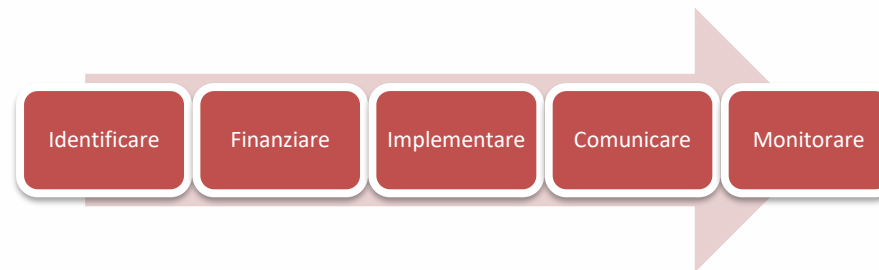
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Sacco, Milano*

*School of Clinical Medicine, Faculty of Health
Science,*

University of the Witwatersrand, Johannesburg

L'innovazione come processo e non come “artefatto”

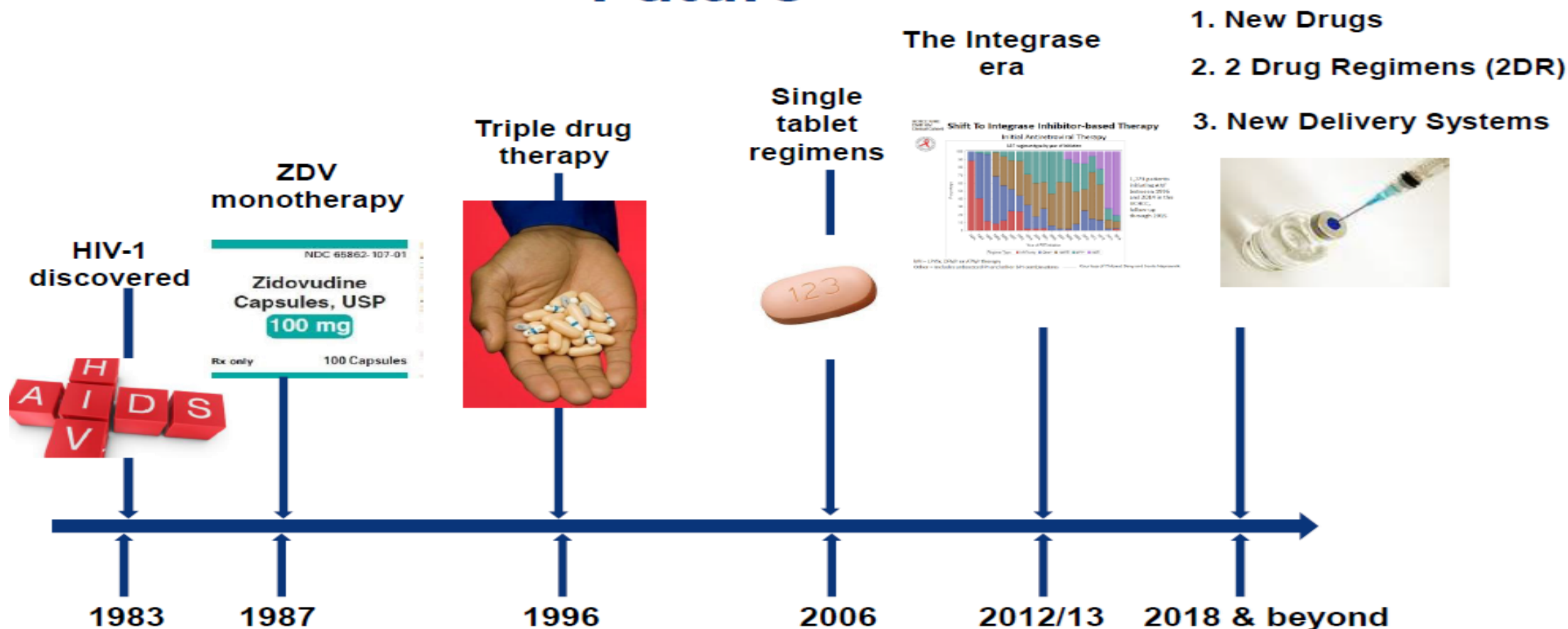


E' “reale” innovazione quella che è in grado di raggiungere la pratica clinica e che può essere utilizzata diffusamente

Solo in questo modo l'innovazione diviene “valore”

Innovazione in HIV. Cosa significa?

Antiretroviral Therapy: Past, Present & Future



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Modern Human Immunodeficiency Virus Therapy: Progress and Prospects

Table 1 Antiretroviral agents approved since 1987

Generic name	Year of approval ⁵⁵
Nucleoside reverse transcriptase inhibitors	
Zidovudine	1987
Didanosine	1991
Zalcitabine ^a	1992
Stavudine	1994
Lamivudine ^b	1995
Abacavir	1998
Tenofovir disoproxil ^b	2001
Emtricitabine ^b	2003
Tenofovir alafenamide ^b	2015
Nonnucleoside reverse transcriptase inhibitors	
Nevirapine	1996
Delavirdine	1997
Efavirenz	1998
Etravirine	2008
Rilpivirine	2011
Doravirine	2018

Protease inhibitors^c

Saquinavir	1995
Indinavir	1996
Ritonavir	1996
Nelfinavir	1997
Amprenavir ^a	1999
Lopinavir ^c	2000
Atazanavir	2003
Fosamprenavir	2003
Tipranavir	2005
Darunavir	2006

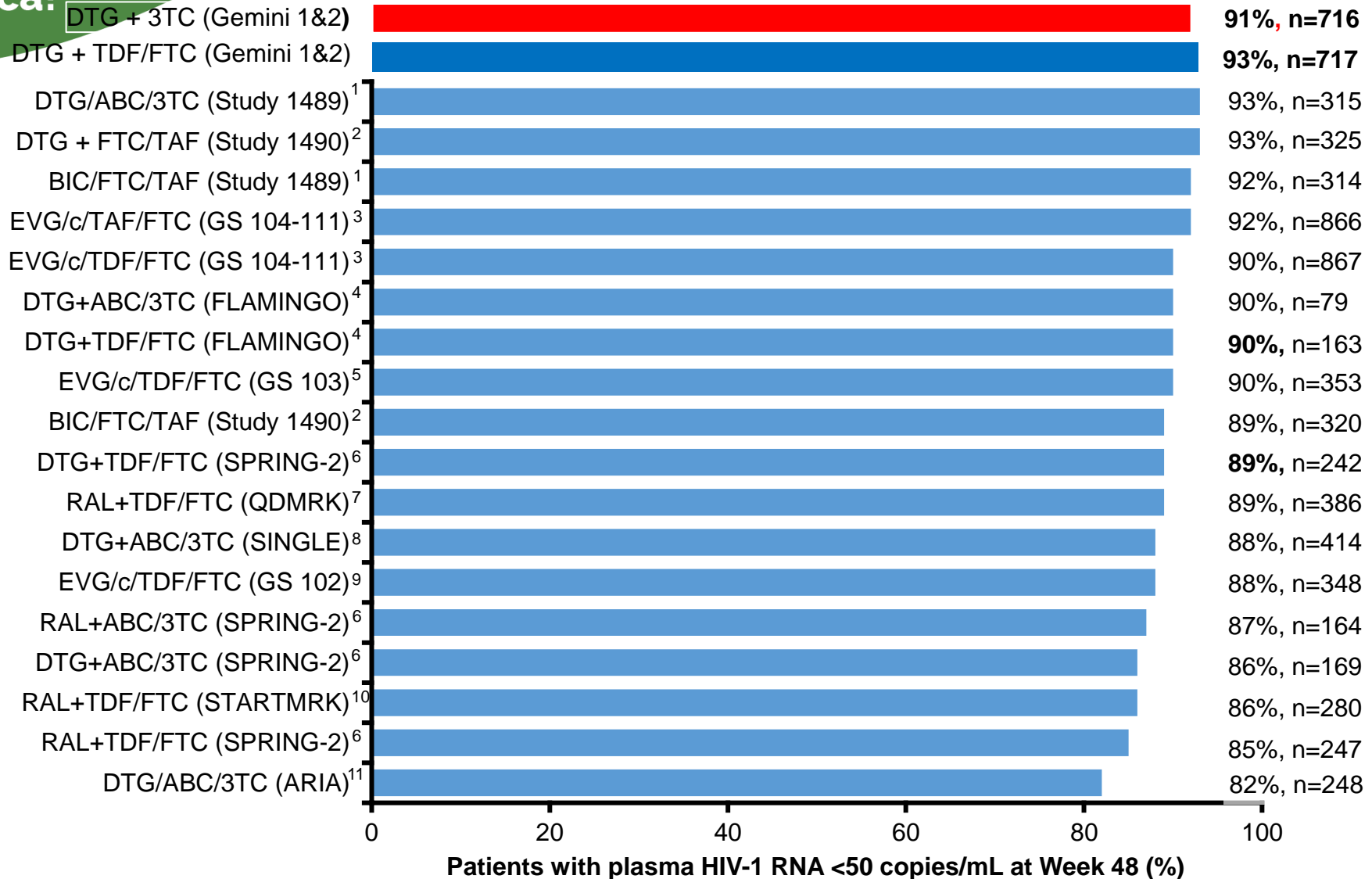
Entry inhibitors

Enfuvirtide	2003
Maraviroc	2007
Albuvirtide ^d	2018
Ibalizumab	2018

Integrase inhibitors

Raltegravir	2007
Elvitegravir ^e	2012
Dolutegravir	2013
Bictegravir ^f	2018

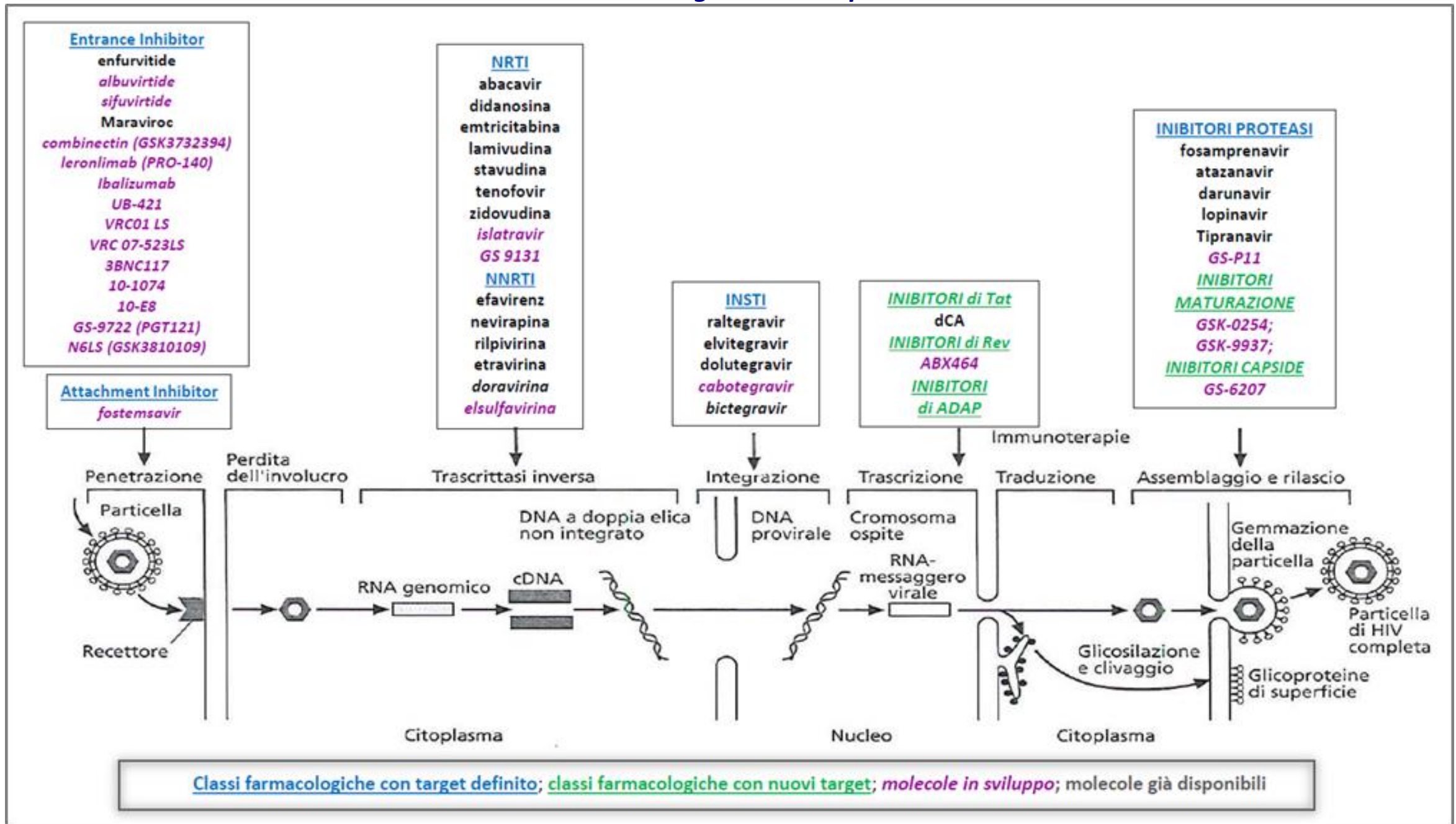
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Note that these data are not intended for cross-study comparisons, but for illustrative purposes only
 3TC = lamivudine; ABC = abacavir; BIC = bictegravir; BID = twice daily; c = cobicistat; DTG = dolutegravir;
 EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor;
 RAL = raltegravir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

See slide notes for references.

Ciclo vitale di HIV e bersagli della terapia antiretrovirale



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Personalizzazione della cART

- The current paradigm in the treatment of HIV involves **life-long therapy with multiple antiretrovirals**.
- Newer antiretrovirals are more potent, better tolerated and have enabled the formulation of **multiple regimens that can provide viral suppression with a single tablet once daily**.

REDUCING DOSE FREQUENCY AND NUMBER OF DRUGS

from «drug burden» to «treatment burden»

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HIV Treatment and management strategies for next 10 yrs

Reducing ART exposure

- ↓ Drug dose
- ↓ Dosing frequency
- ↓ Number of drugs

New agents

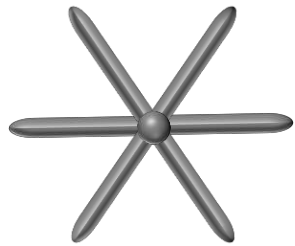
- Investigational ARTs
- Monoclonal antibodies

Different ART formulations

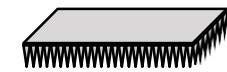
- Long-acting oral
- Implantable
- Long-acting injectable

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What are the long-acting technologies?



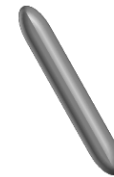
Gastric residence device



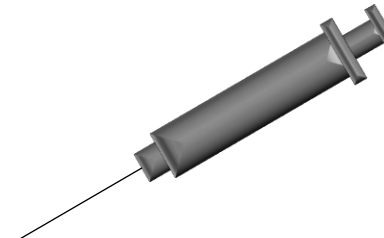
Microarray /
microneedle patch
(theoretical)



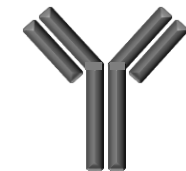
Vaginal ring



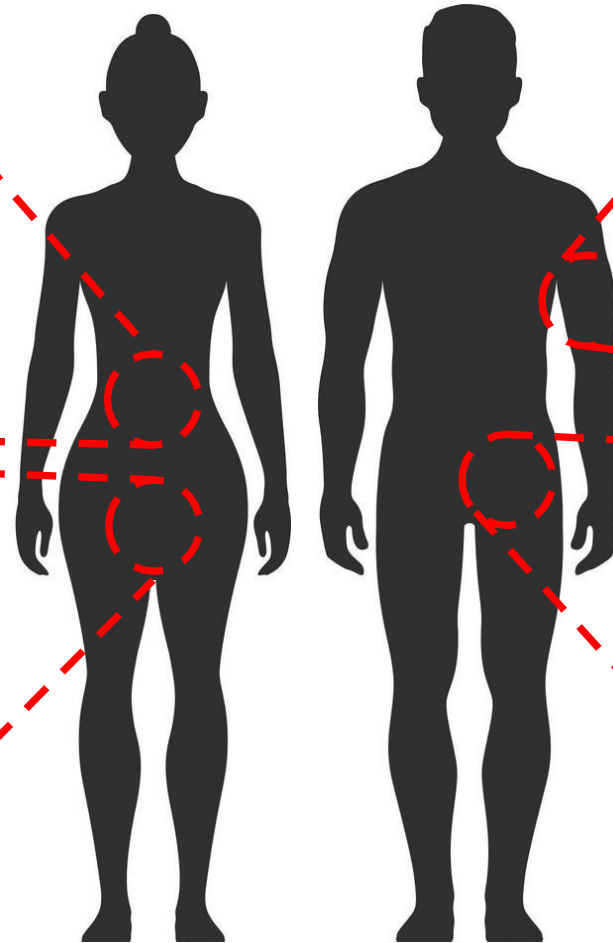
Implant



Injectable drug



Broadly neutralizing
monoclonal
antibodies



HIV Drug Pipeline in clinical development: modes of delivery

ORAL

**Fostemsavir
FTR**

**Cenicrivir
oc
CVC**

ABX464

bictegravir

Cabotegravir

doravirine

**Islatravir
(MK8591)**

GSK0254

GSK9935A

elsulfavirine

GS-P11

MK-8507

INJECTABLE

albuvirtide

ibalizumab

PRO-140

**Sifuvirtide
(FS-0101)**

UB-421

VRC-01

VRC-07

**GSK2394
Combivir
in**

OTHER (TOPICAL, IMPLANTABLE, GEL)

dapivirine

MK-2048

**Pc-1005
MIV150
z.ac**

LONG-ACTING INJECTABLE

**bnAbs LA
(VRC-07 523 LS
GSK109 N6-LS)**

GSK9937

CAB-LAI

**Islatravir
(MK8591)**

RPV-LAI

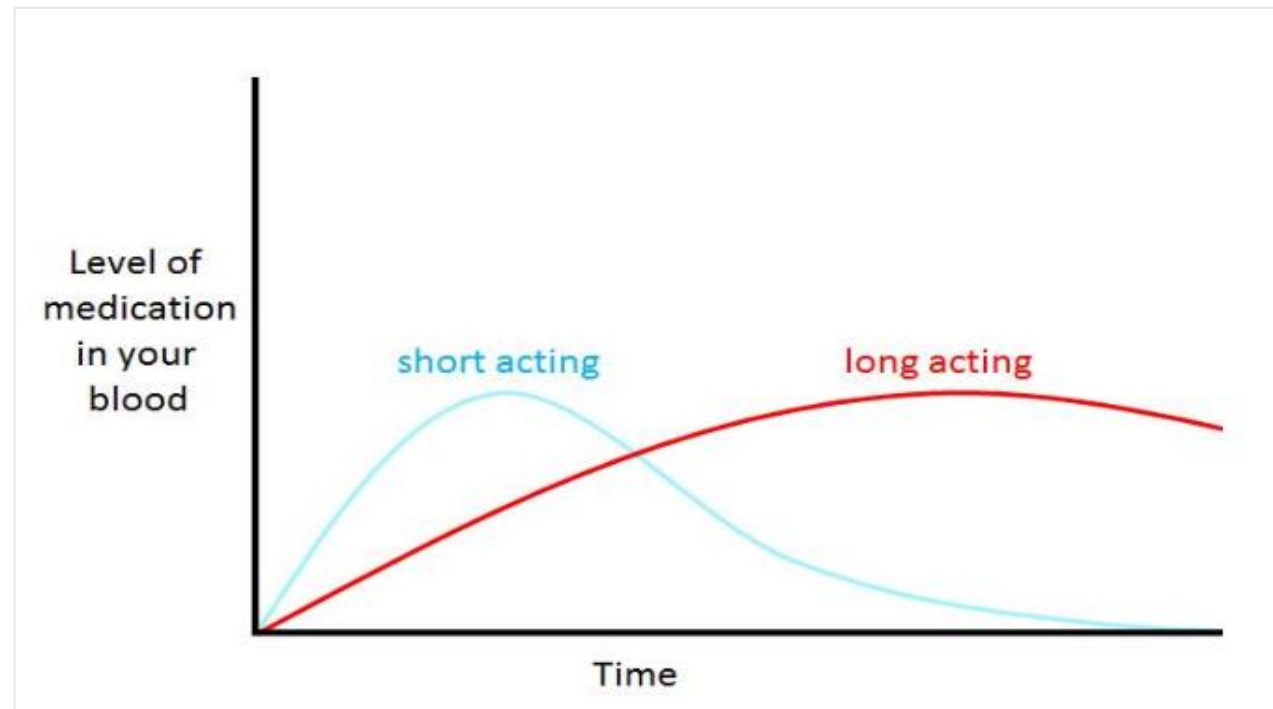
GS-9131

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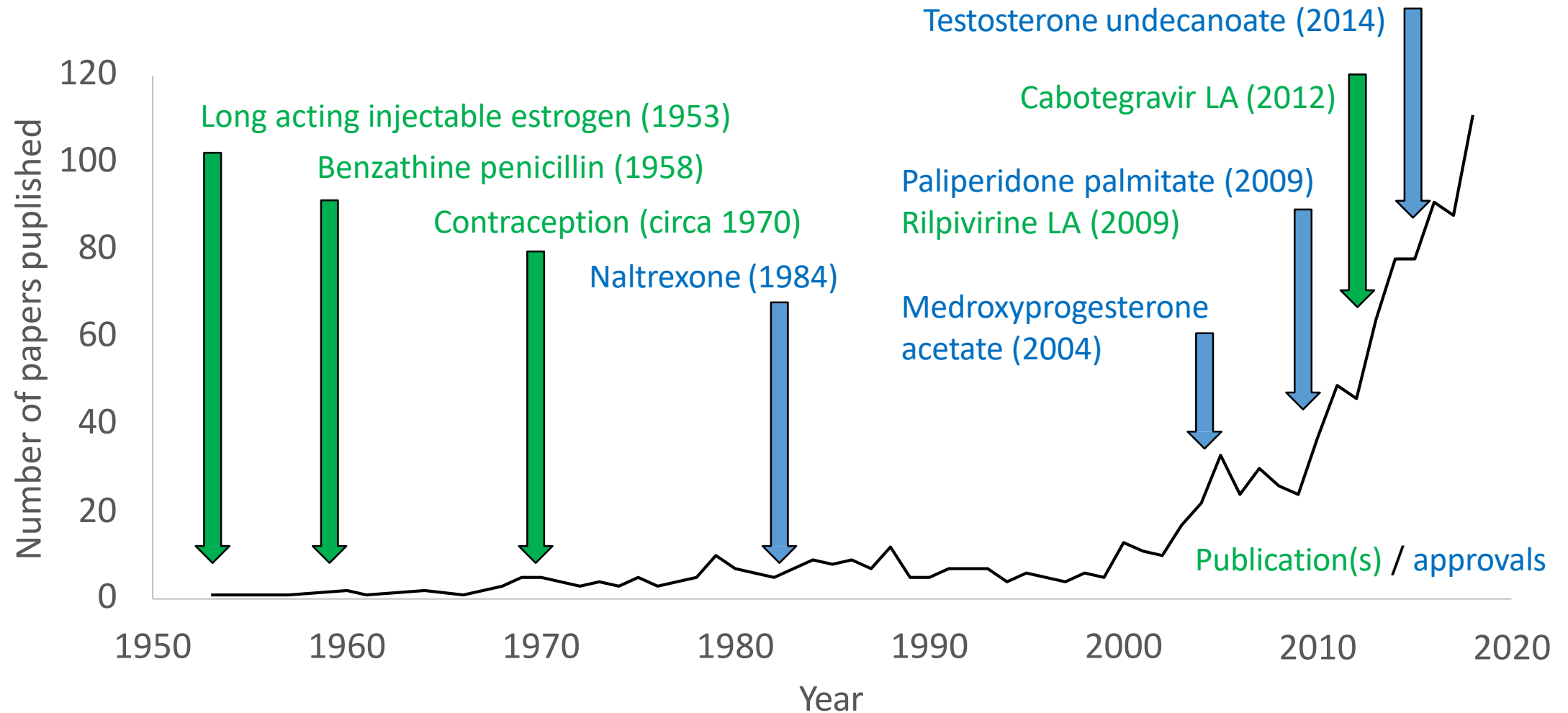
Long-acting: definition

Drug with a **prolonged effect** because of **formulation**.

Slow **release** of active principle and/or continued **absorption** of the drug over an extended time



Long-acting injectables / parenterals: brief history

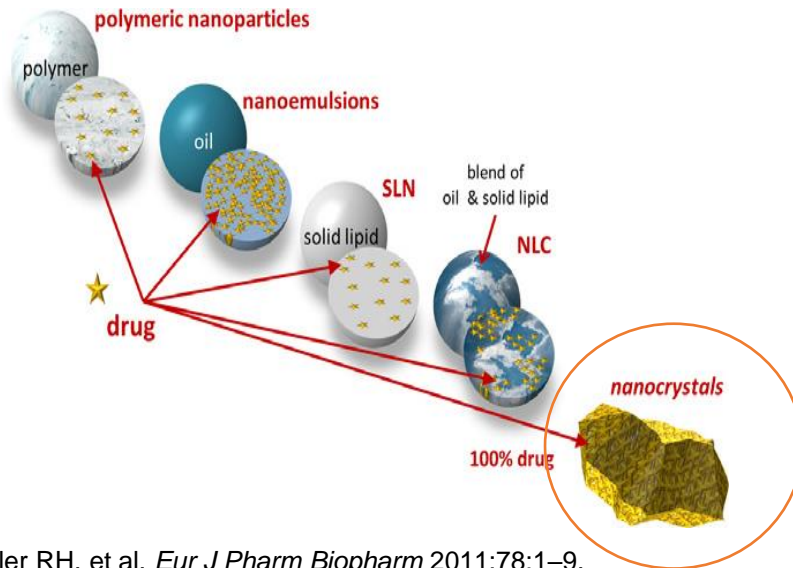


Using Pubmed search term: "long acting injectable" OR "long acting parenteral" OR "long acting depot"

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CAB LA formulation allows for lower injection volumes

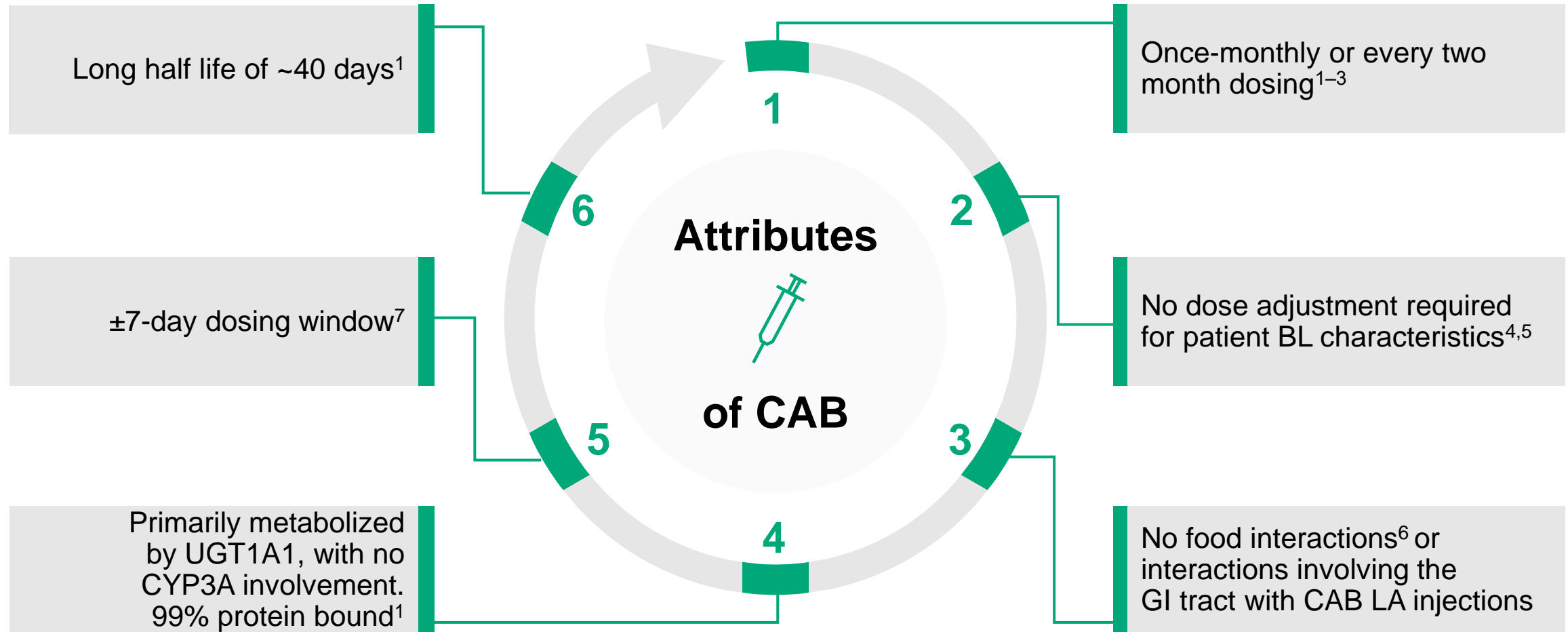
- Drug crystal suspended in aqueous vehicle^{1,2}
- Milled to nanometer size to increase surface area and drug dissolution rate^{1,2}
- Higher drug loading versus matrix approaches for lower injection volume^{1,2}



Müller RH, et al. *Eur J Pharm Biopharm* 2011;78:1–9.

CAB LA 200 mg/mL ²	
Component	Function
Cabotegravir free acid (d50 ~200 nm)	Active drug
Mannitol	Tonicity agent
Surfactant system	Wetting agent/stabiliser
Water for injection	Solvent

Pharmacological attributes of CAB LA



CAB + RPV LA combines two different LA injectable ARVs

- / CAB LA and RPV LA are extended release suspensions that enable monthly dosing^{1,2}
- / CAB and RPV have a number of important attributes that support their use as a LA combination therapy:^{1–3}
 - / Different MoA and resistance profiles
 - / Lack of DDI between CAB and RPV
 - / Oral formulations of both drugs facilitate treatment initiation and oral bridging

Attribute	CAB LA ^{1,4,5}	RPV LA ^{3–5}
ARV drug class	INI	NNRTI
Oral tablet size (t _{1/2})	30 mg (41 hours)	25 mg (~50 hours)
LA suspension (t _{1/2})	200 mg/mL (5.6–11.5 weeks)	300 mg/mL (13–28 weeks)
Dose – monthly	400 mg (2 mL)	600 mg (2 mL)
Dose – every 2 months	600 mg (3 mL)	900 mg (3 mL)



Cabotegravir (CAB) & Rilpivirine (RPV) Long-acting characteristics: CARLA

- CAB Oral 30 mg ($t_{1/2}$, ~40 hours)
- CAB LA nano 200 mg/mL ($t_{1/2}$, ~20-40 days)
- RPV Oral 25 mg ($t_{1/2}$, ~50 hours)
- RPV LA nano 300 mg/mL ($t_{1/2}$, ~30-90 days)
- Oral 2-drug CAB + RPV proof of efficacy through Week 96 in LATTE-1
- im 2-drug CAB + RPV maintained VL < 50 in LATTE 2*



Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial

Dr David A Margolis, MD  , Juan Gonzalez-Garcia, MD, Prof Hans-Jürgen Stellbrink, MD, Prof Joseph J Eron, MD, Prof Yazdan Yazdanpanah, MD, Daniel Podzamczek, PhD, Thomas Lutz, MD, Jonathan B Angel, MD, Gary J Richmond, MD, Bonaventura Clotet, MD, Prof Felix Gutierrez, MD, Prof Louis Sloan, MD[†], Marty St Clair, BS, Miranda Murray, PhD, Susan L Ford, PharmD, Joseph Mrus, MD, Parul Patel, PharmD, Herta Crauwels, PhD, Sandy K Griffith, Pharm D, Kenneth C Sutton, MA, David Dorey, MMath, Kimberly Y Smith, MD, Peter E Williams, PhD, William R Spreen, Pharm D

[†] Prof Louis Sloan died in June, 2017

Published: 24 July 2017

CAB, cabotegravir; LA, long-acting; RPV, rilpivirine; $t_{1/2}$, half-life.

Margolis et al. *Lancet Infect Dis.* 2015;15:1145-1155. Margolis et al. *AIDS* 2016; Durban, South Africa. Abstract THAB0206LB; Slide modified from Viiv Healthcare.

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Nanomedicine - size



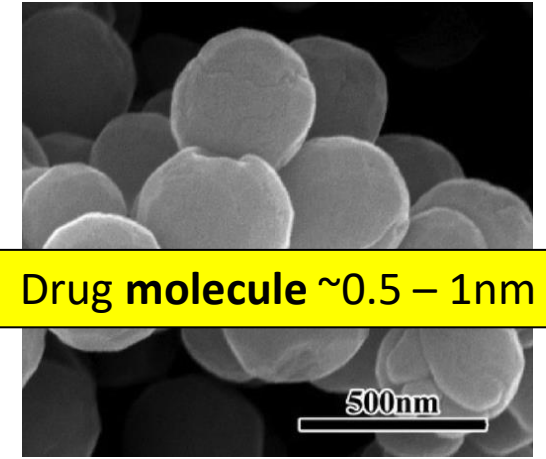
Colosseum diameter:
190 metres



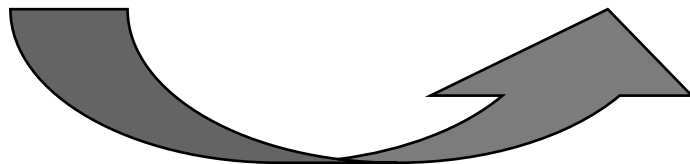
Football diameter:
22 centimetres



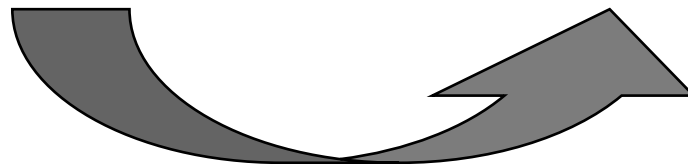
Espresso grind particle diameter:
250 micrometres



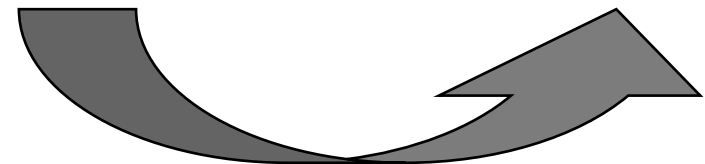
Droga nanoparticella:
500-200 nanometres



Approximately 863-times
smaller



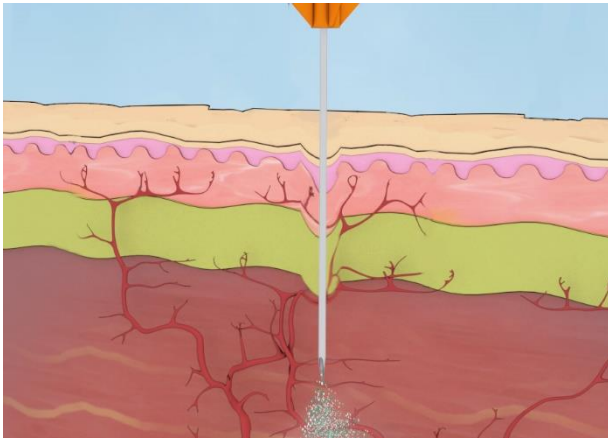
Approximately 863-times
smaller



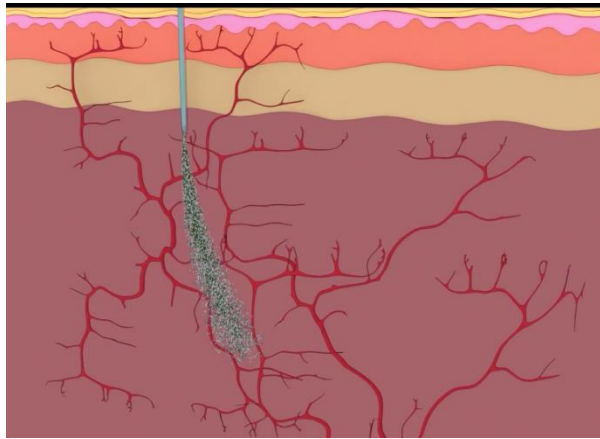
Approximately-863 times
smaller

CAB + RPV LA formulation allows for monthly or every 2-month dosing

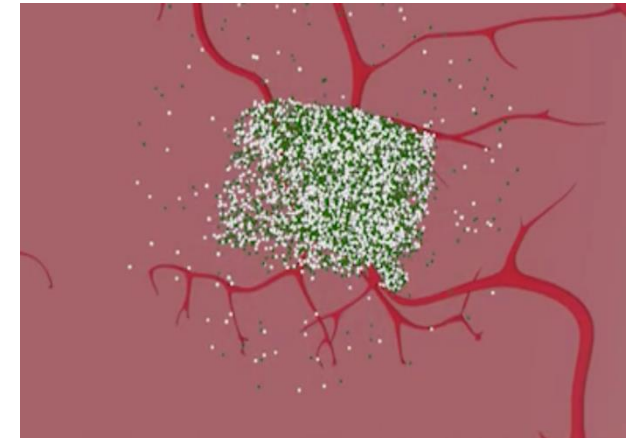
- / CAB + RPV extended-release suspensions contain finely-milled drug particles suspended in an aqueous vehicle that supports LA dosing:



CAB + RPV LA is administered via IM gluteal injection



LA suspension forms a drug depot in the muscle

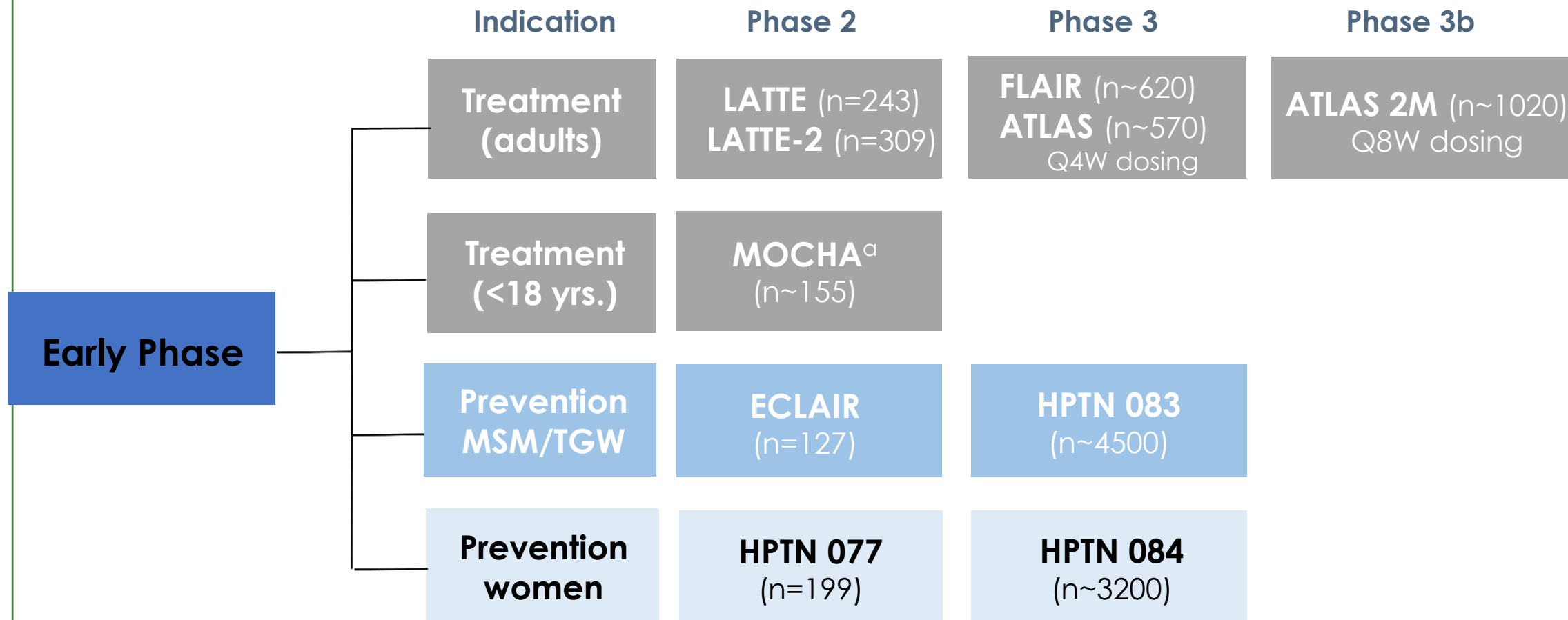


Medications are slowly absorbed from the depot site into the bloodstream

Formulations allow for continuous drug exposure that lasts over the duration of a one-month or two-month dosing interval

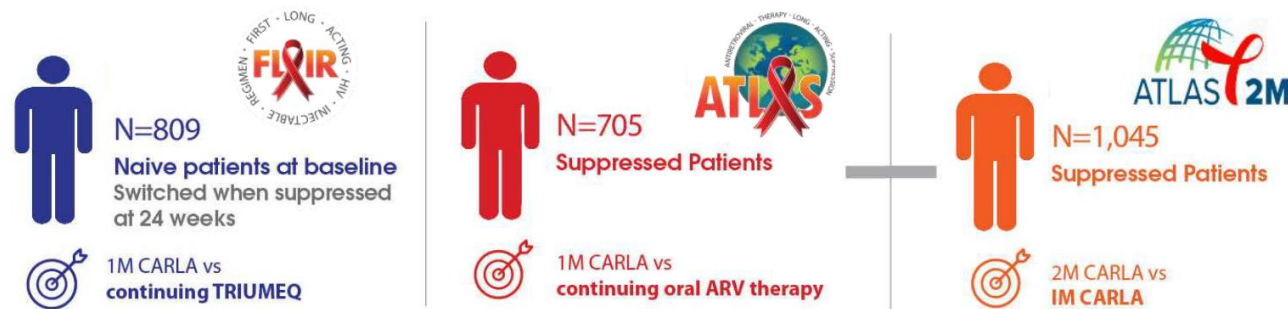
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Simultaneous Global Registration Programs for Treatment and Prevention



^a MOCHA (IMPAACT 2017) Phase 1/2 study will provide supportive information for HIV prevention in adolescents

CARLA Phase III Trials Overview



Non-inferior to Standard of Care

Approval timeline

	FDA	EMA	ITALY
CARLA	Priority Rev Design. Exp approval: 29th Dec 2019	Submitted July2019 Exp approval: July2020	Submission July2020? Exp approval: July2021?

PRESS RELEASE

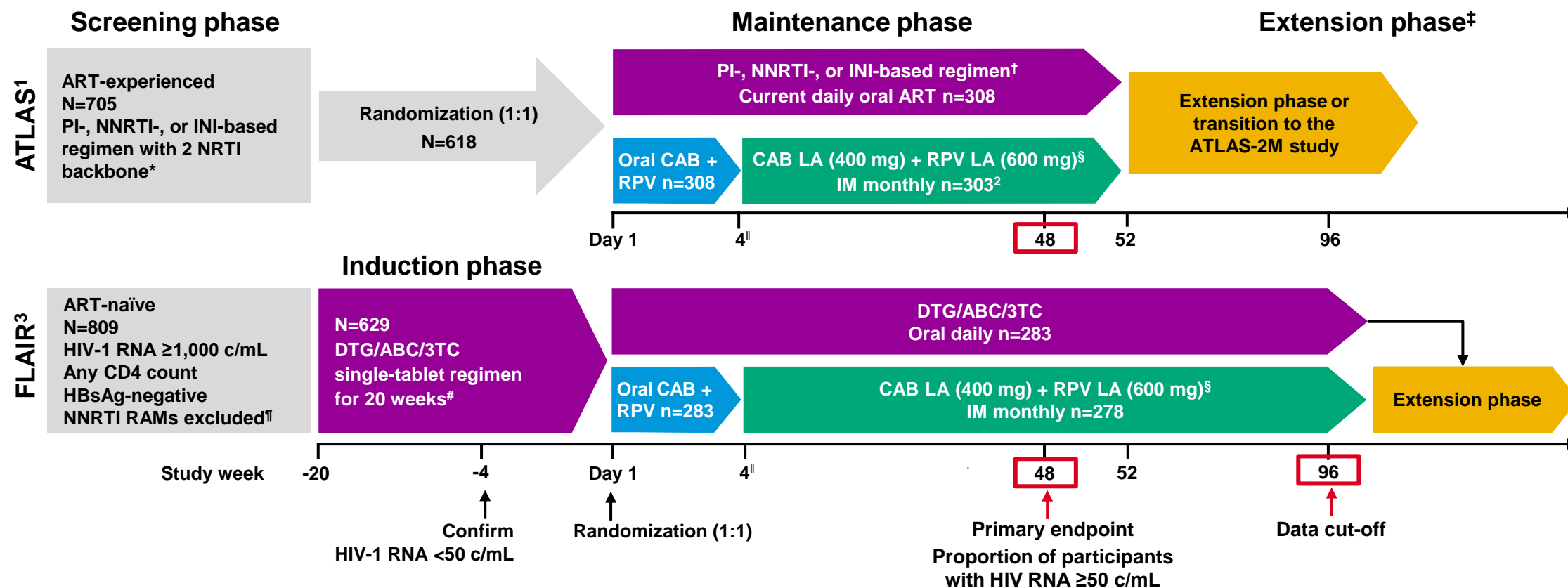
ViiV Healthcare reports positive phase III study results of investigational, long-acting, injectable HIV-treatment regimen administered every two months

ATLAS-2M study met its primary endpoint, showing similar efficacy of cabotegravir and rilpivirine administered every eight weeks compared to four-week administration

London, 22 August 2019 – ViiV Healthcare, the global specialist HIV company majority owned by GSK, with Pfizer Inc. and Shionogi Limited as shareholders, today announced positive headline results from its global phase III ATLAS-2M study of the investigational, long-acting, injectable, 2-drug regimen (2DR) of ViiV Healthcare's cabotegravir and Janssen's rilpivirine for the treatment of HIV. The study was designed to demonstrate the non-inferior antiviral activity and safety of long-acting cabotegravir and rilpivirine

ATLAS and FLAIR: Study designs

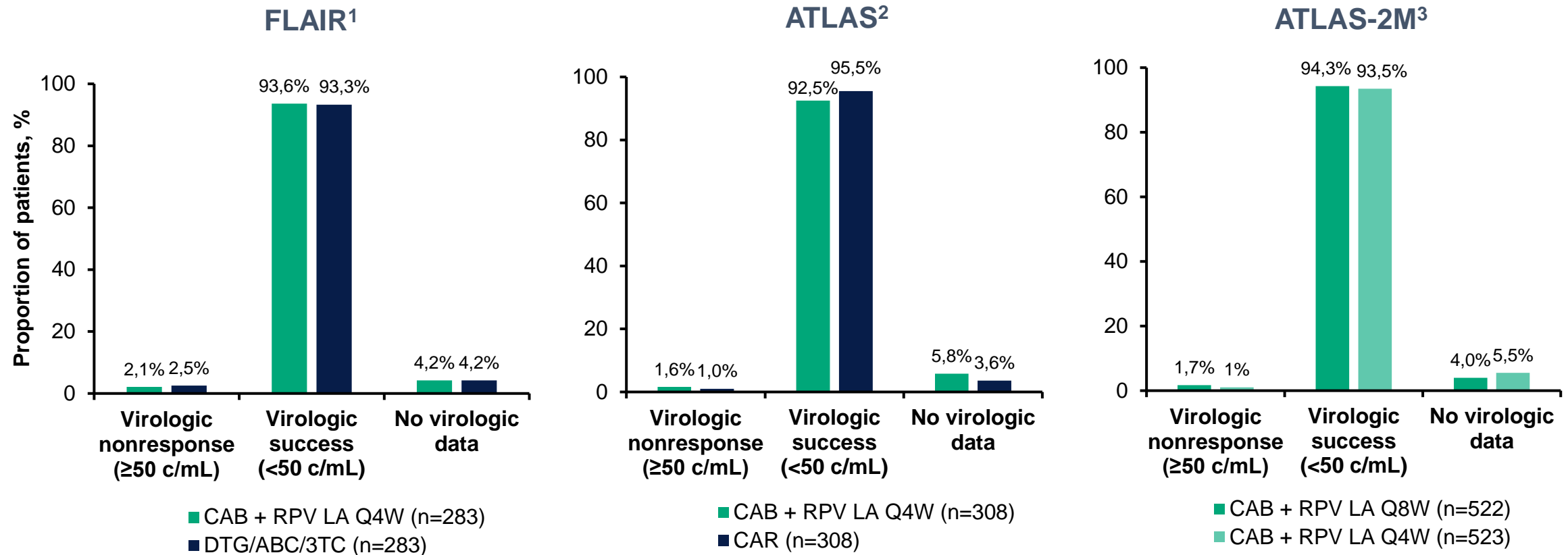
Phase III, randomized, multicenter, international, open-label, non-inferiority studies



*Uninterrupted ART for 6 months and VL <50 c/mL at screening, 2 x VL <50 c/mL ≤ 12 months; [†]INI-based regimen capped at 40% of enrolment. Trimeq excluded from study; [‡]Optional switch to CAB + RPV LA at Week 52 for those on CAR; [§]Participants who withdraw/complete IM CAB + RPV LA must complete 52 weeks of follow-up; ^{||}Participants received an initial loading dose of CAB LA (600 mg) and RPV LA (900 mg) at Week 4. From Week 8 onwards, participants received CAB LA (400 mg) + RPV LA (600 mg) injections every 4 weeks; [¶]NNRTI RAMs except K103N were excluded; [#]DTG plus two alternative non-ABC NRTIs was permitted if participant was intolerant or HLA-B*5701-positive
3TC, lamivudine; **ABC**, abacavir; **ART**, antiretroviral therapy; **CAR**, current ARV regimen; **DTG**, dolutegravir; **HBsAg**, hepatitis B surface antigen
HLA, human leukocyte antigen; **NRTI**, nucleoside reverse transcriptase inhibitor; **PI**, protease inhibitor; **RAM**, resistance-associated mutation; **VL**, viral load

CAB + RPV LA Q4W or Q8W dosing has shown non-inferior efficacy versus comparator arms in Phase III trials to Week 48

Virologic Snapshot outcomes at Week 48 (ITT-E)*



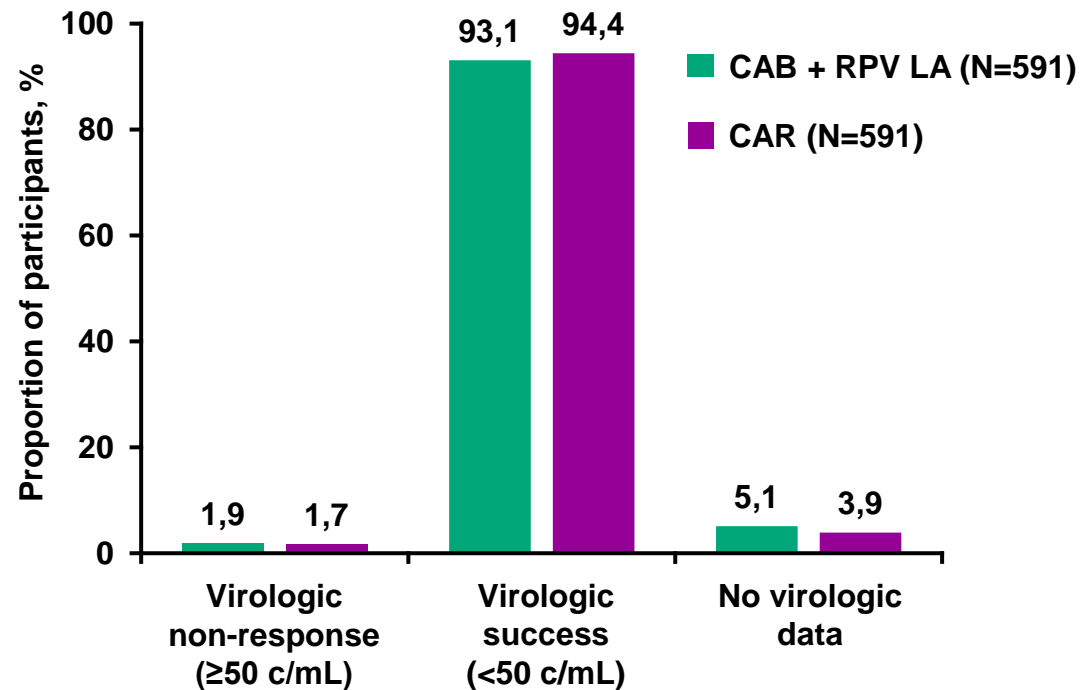
*Primary endpoint: noninferiority (HIV-1 RNA ≥50 c/mL) to comparator arm; key secondary endpoint: noninferiority (HIV-1 RNA <50 c/mL) to comparator arm

1. Orkin C, et al. N Engl J Med 2020;382:1124–35
2. Swindells S, et al. N Engl J Med 2020;382:1112–23
3. Overton ET, et al. CROI 2020. Oral 3334

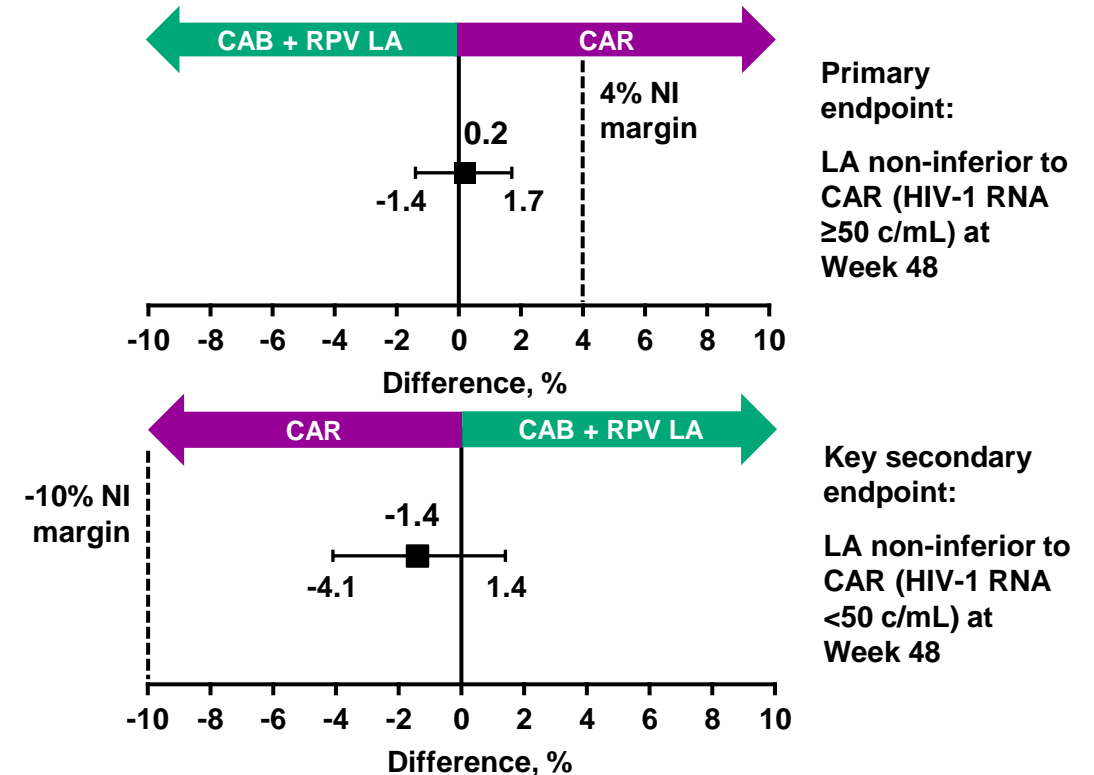
ATLAS and FLAIR: Pooled virologic Snapshot outcomes at Week 48 (ITT-E)



Virologic outcomes



Treatment differences (95% CI)*



CAB + RPV LA achieved non-inferiority versus CAR for the primary endpoint of HIV-1 RNA ≥ 50 c/mL at Week 48

*Adjusted for sex and BL third-agent class
CI, confidence interval; NI, non-inferiority

ATLAS and FLAIR: Pooled safety overview through Week 48 in the maintenance phase (excludes ISRs)

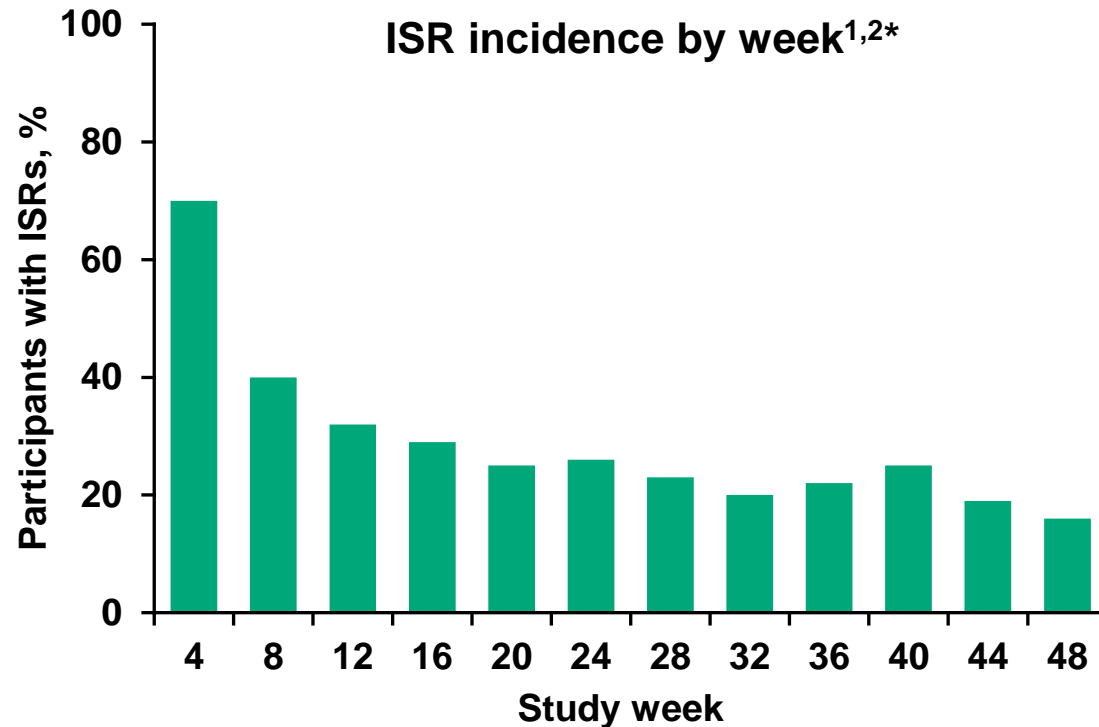


n (%)	CAB + RPV LA N=591	CAR N=591
Any AE	506 (86)	444 (75)
Any Grade ≥ 3 AE*	44 (7)	35 (6)
Any drug-related AE	165 (28)	35 (6)
Any Grade ≥ 3 drug-related AE*	8 (1)	1 (<1)
Any AEs leading to withdrawal	17 (3)	9 (2)
Any serious AE	24 (4)	25 (4)
Serious AEs related to study treatment	1 (<1)	1 (<1)
Common AEs ($\geq 5\%$)		
Nasopharyngitis	108 (18)	90 (15)
Headache	73 (12)	38 (6)
Upper respiratory tract infection	70 (12)	53 (9)
Diarrhea	54 (9)	40 (7)
Back pain	43 (7)	23 (4)
Influenza	42 (7)	34 (6)
Pyrexia	43 (7)	13 (2)
AEs of special interest		
Anxiety	27 (5)	20 (3)
Depression	16 (3)	14 (2)
Suicidal ideation/behavior	4 (<1)	5 (<1)

**Most drug-related AEs were Grade 1 or 2, and mild-to-moderate in severity.
There was no pattern of events leading to treatment discontinuation**

*There was only one (<1%) participant with a Grade 5 AE, in the CAR arm
AE, adverse event; ISR, injection-site reaction

ISRs were common with CAB + RPV LA, though most were mild and incidence declined over time



Event	CAB + RPV LA ^{1,2} N=591
Participants receiving injections, n	581
Injections given, n (%)	14,682
ISR events	3,663 (24.9)
Pain	3,087 (21.0)
Nodule	140 (1.0)
Induration	136 (0.9)
Swelling	86 (0.6)
Grade 3 ISR pain	32 (0.2)
Median duration of ISR, days	3
Participants with ISR leading to withdrawal, n (%)	6 (1)

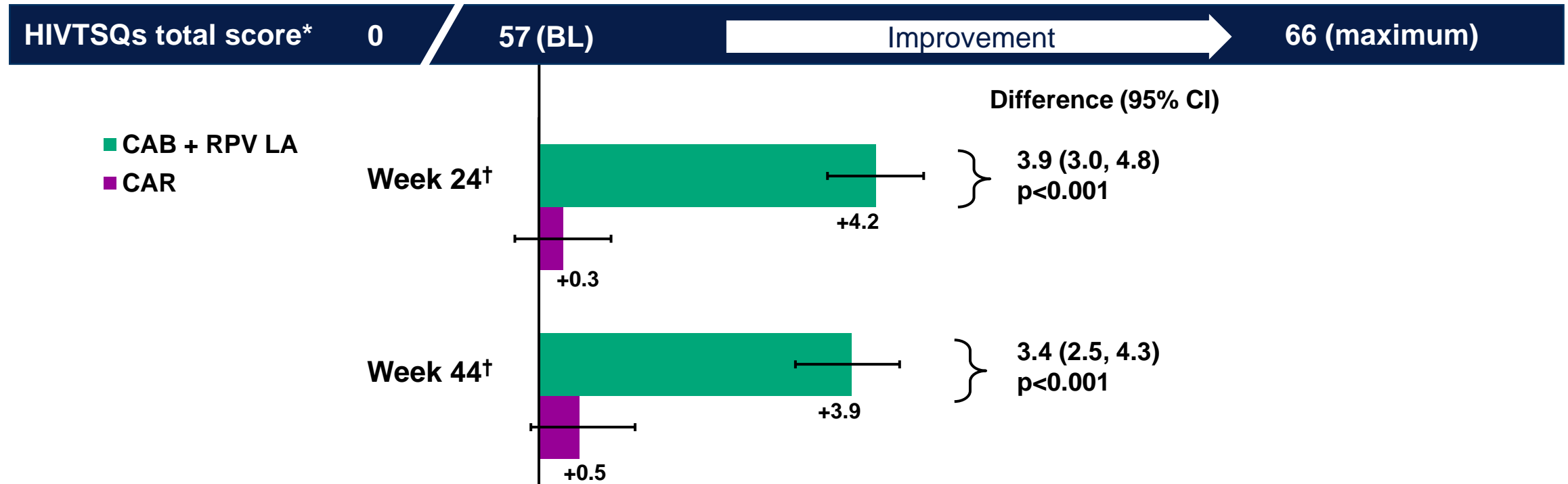
- / The majority of participants (55%) reported ≤ 3 injection pain events over the 48-week treatment period²
- / 85% of CAB + RPV LA participants rated pain as 'totally/very acceptable' at Week 48, as assessed by PIN²

~25% of injections were associated with ISRs, the majority (99%) being Grade 1 or 2, with a median duration of 3 days. Only 1% of participants discontinued due to ISRs¹

*Bars represent incidence of onset ISRs relative to the most recent LA injection visit
PIN, perception of injection questionnaire

1. Overton ET, et al. IAS 2019. Poster MOPEB257
2. Teichner P, et al. IDWeek 2019. Oral 884

ATLAS and FLAIR: Pooled change in treatment satisfaction from baseline (HIVTSQs)



CAB + RPV LA participants demonstrated significantly greater improvement in treatment satisfaction from BL versus CAR participants at Weeks 24 and 44

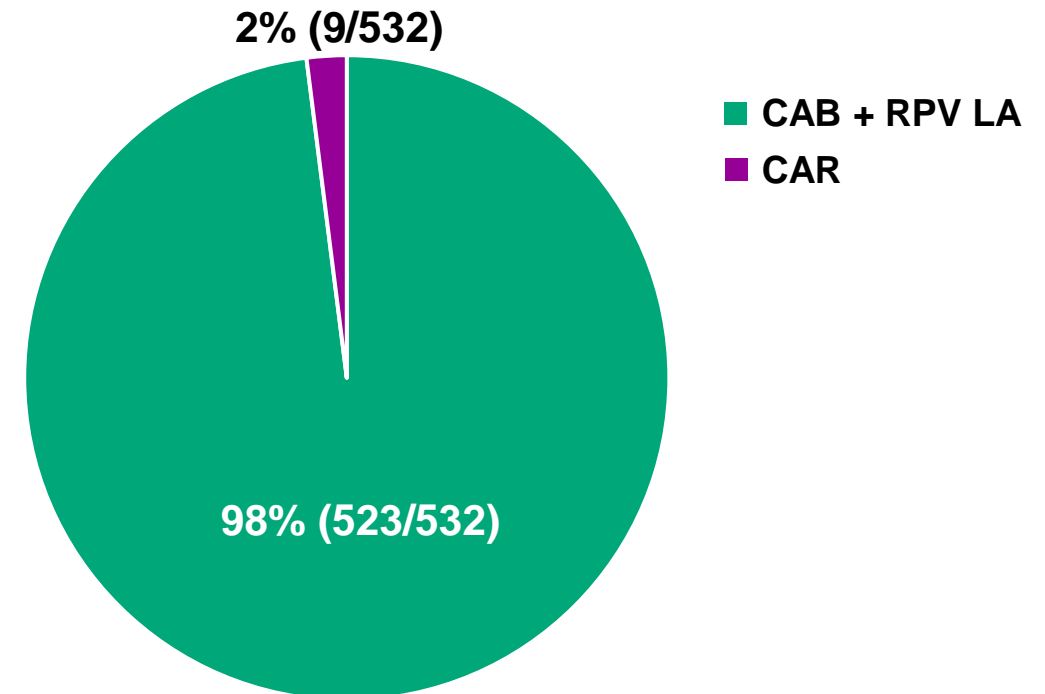
Pooled ATLAS and FLAIR: CAB + RPV LA was preferred over daily oral ART



Preferences of responding participants*^{1,2}

“For the past 44 weeks you have received long-acting injectable HIV medication every month. Today we would like you to compare your experience on the long-acting injections with the oral medication you received during the induction phase of the study.

Which therapy do you prefer?”¹



98% of responding participants from ATLAS + FLAIR preferred CAB + RPV LA over CAR at Week 48²

*Responding participants: 98% (523/532) preferred the LA regimen over previous oral therapy

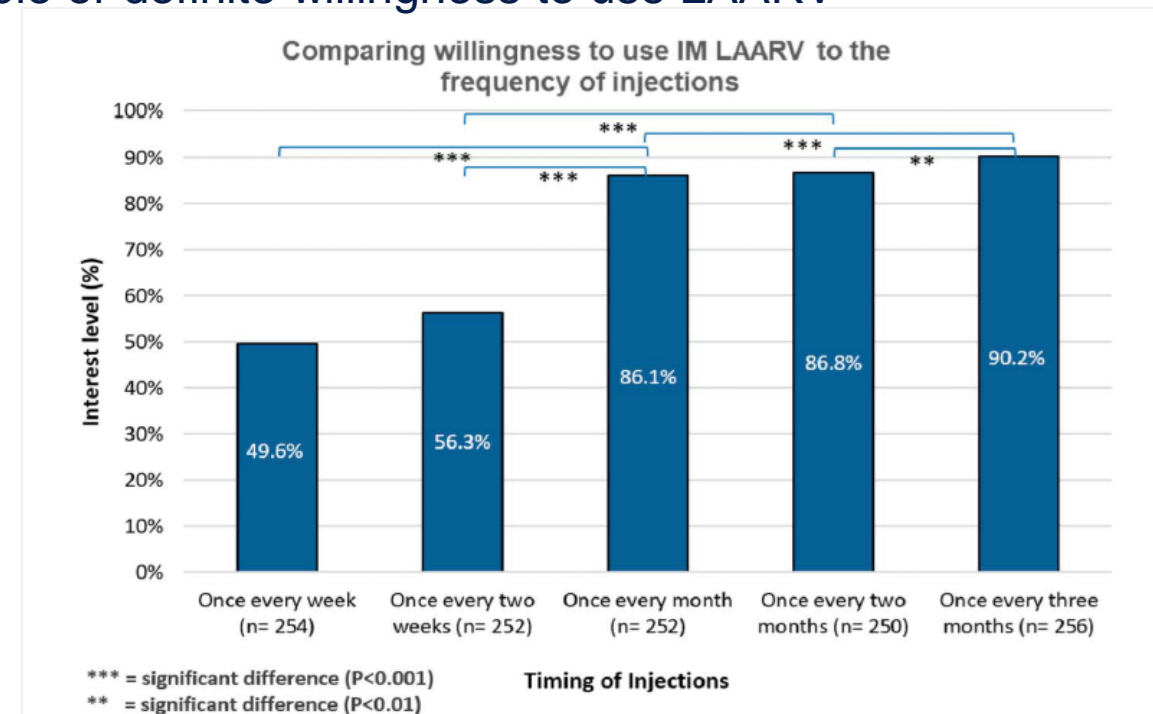
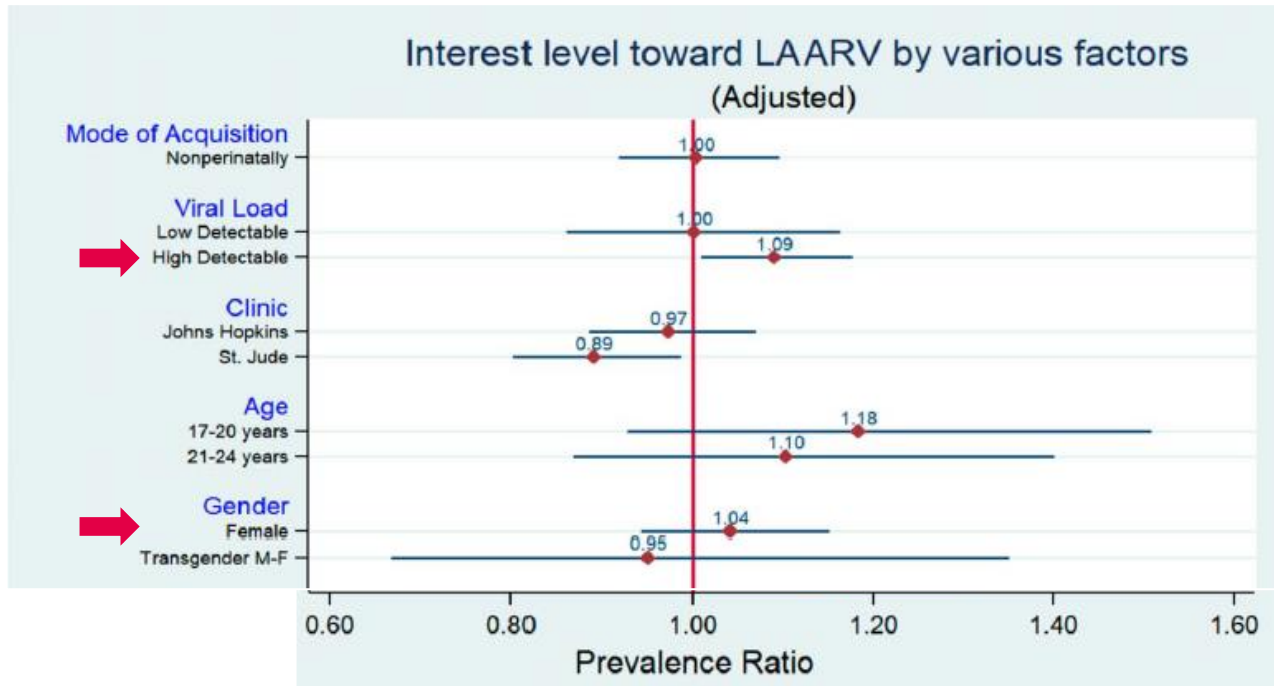
1. Murray M, et al. AIDS Behav 2020; doi: 10.1007/s10461-020-02929-8 (online ahead of print)

2. Overton ET, et al. IAS 2019. Poster MOPEB2578

Interest of Youth Living With HIV in Long-Acting Antiretrovirals

This study's primary objective was to characterize **attitudes** to long-acting antiretrovirals (LAARV), among youth **aged 13–24 years** living with perinatally acquired HIV and nonperinatally acquired HIV.

Overall, **88%** of YHIV (n=303) reported probable or definite willingness to use LAARV



Lifelong daily HIV therapy can be challenging for some PLHIV



Fear of disclosure¹⁻³

Stigma surrounding HIV is a major concern for PLHIV, and disclosure of HIV status is perhaps the area an individual retains the greatest control



"Whenever I go out with [my friends] or they come over to visit, I don't take my medications. I could never let them know I'm positive"³



Daily reminder of HIV²

Psychological challenges can match physical manifestations



"I'm telling you it's very depressing, you got to take it every day, every day, every day, and that's not every day living. And sometimes you want to say Lord, I want to take a break. I'm tired of taking pills"⁴



Adherence anxiety²

Daily medication can be restrictive and may lead to **adherence anxiety**

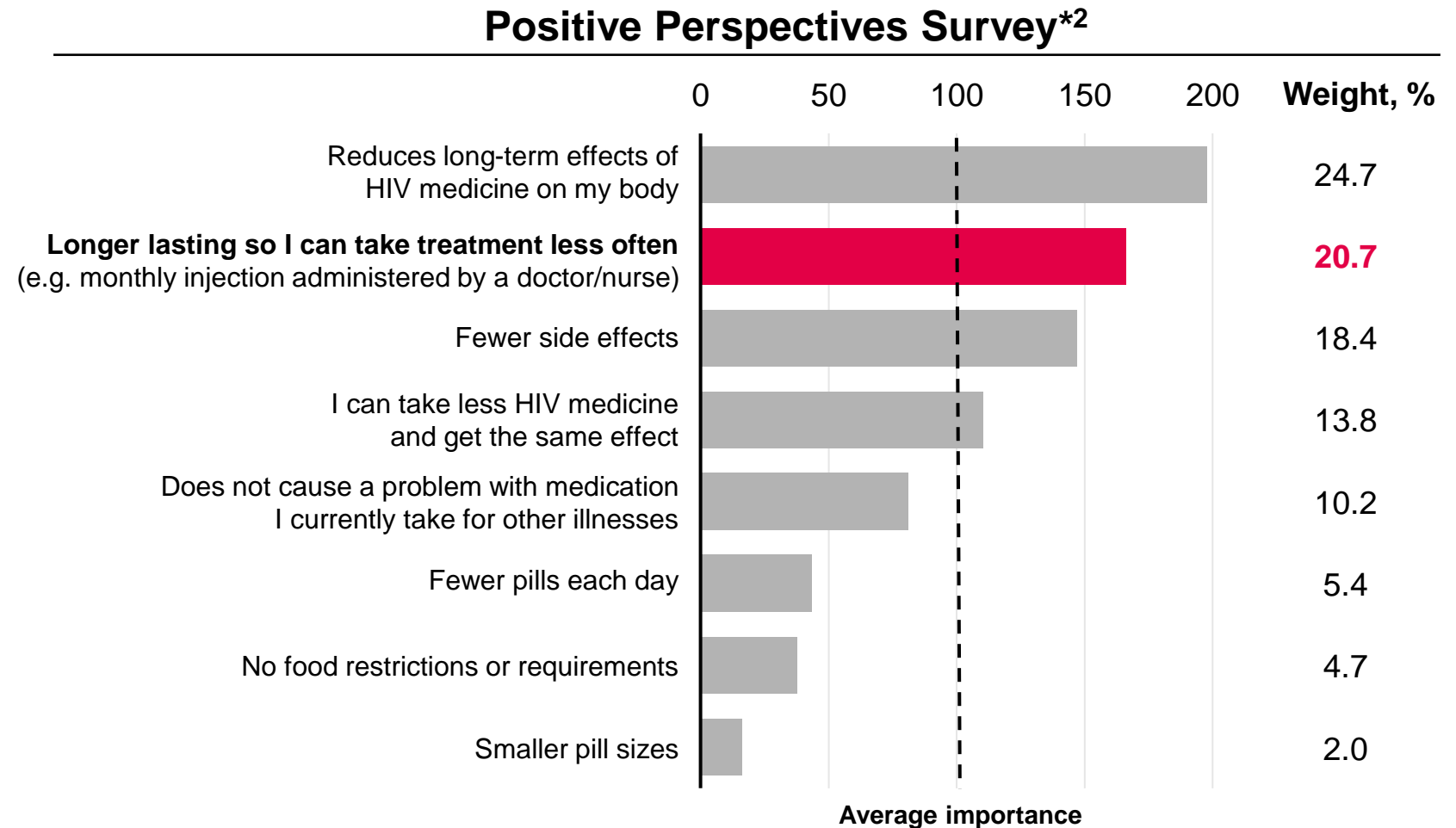


"...I'd still get anxiety over whether I'd taken it or not, and once or twice I double-dosed, just because I couldn't remember, but then I'd go count and – it's just a lot of anxiety..."⁵

Patient surveys have identified long-lasting treatment, requiring less frequent dosing, as a priority for PLHIV

/ Treatments need to fit in with an individual patient's routine, expectations, and preferences¹

/ Long-lasting treatment, requiring less frequent dosing, is one of the most important unmet needs for PLHIV – more so than reduction of side effects and pill burden²

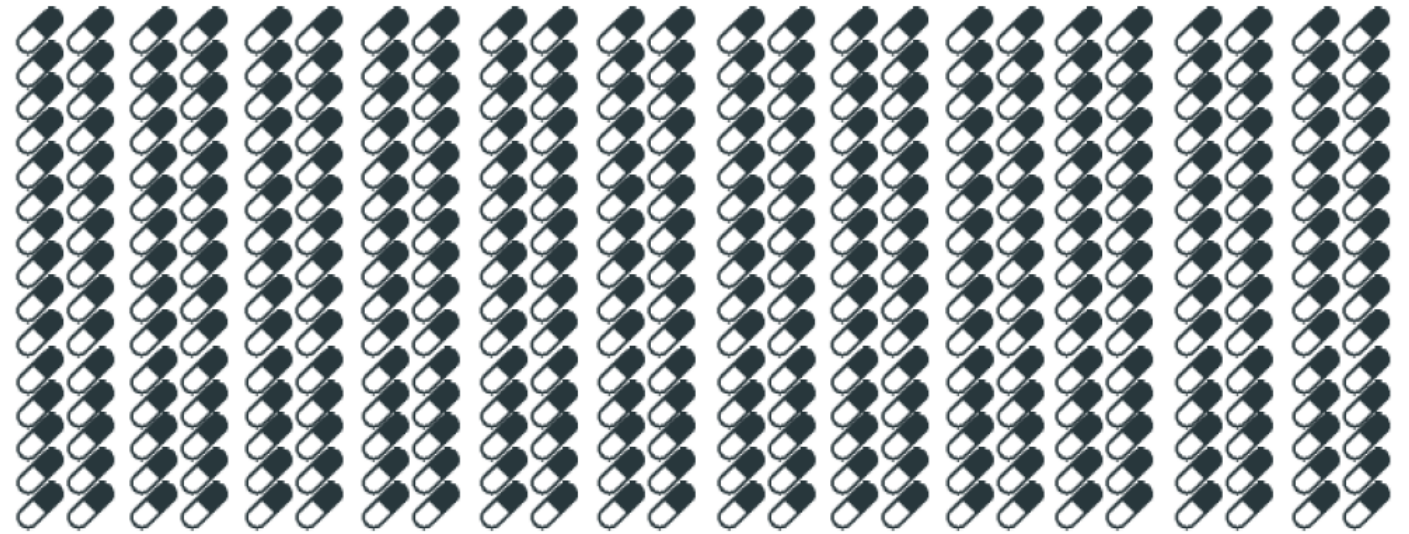


*The Positive Perspectives Survey was conducted between 2016 and 2017 in nine countries. Participants were enrolled from North America, Europe, and Australia (N=1,111)

1. DHHS. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Dec 2019
2. Young B, et al. IDWeek 2017. Poster 1393

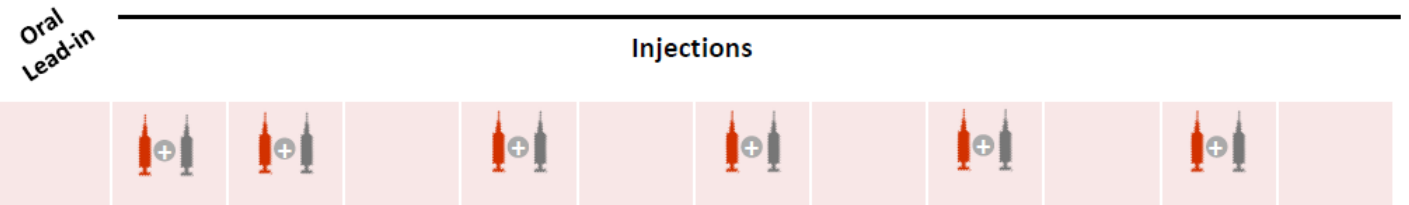
One Year Of HIV Therapy

Daily ARV therapy*



Month 1 2 3 4 5 6 7 8 9 10 11 12

The first, and only, complete long acting regimen for the treatment of HIV

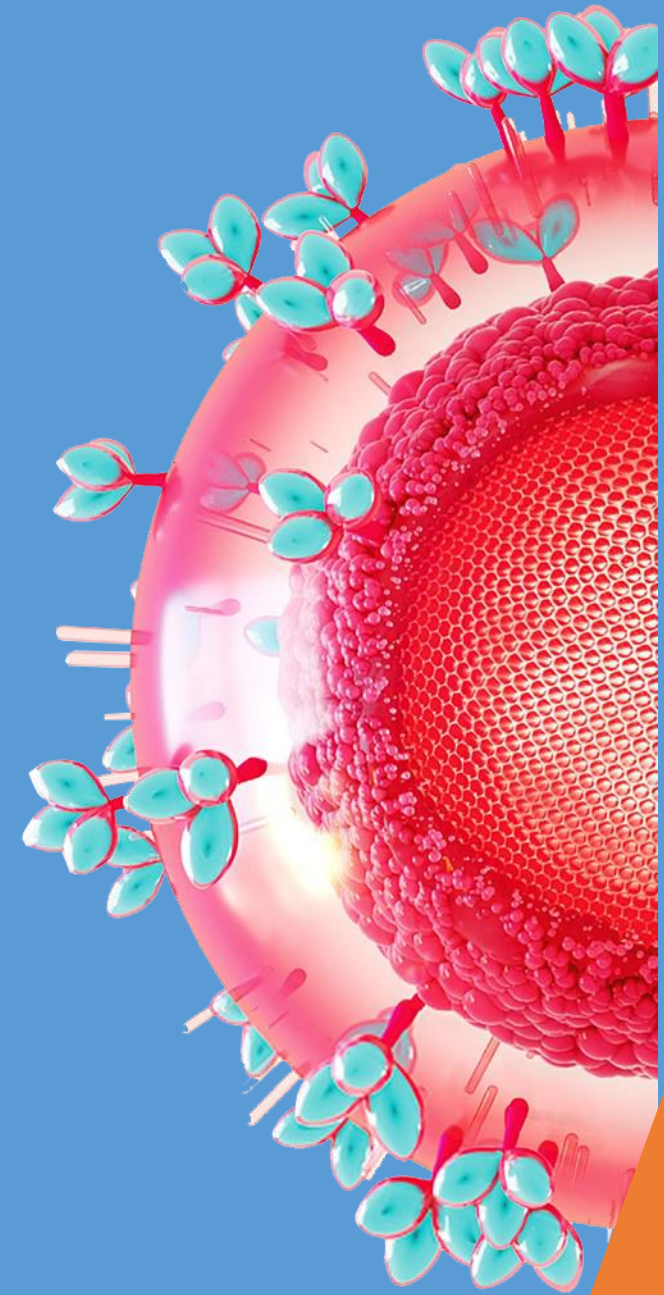


Q2M
30mg CAB
25mg RPV
600 mg CAB
900 mg RPV



*Represents daily intake of medication and not necessarily the actual number of tablets

The changing face of
treatment → The changing
face of organization

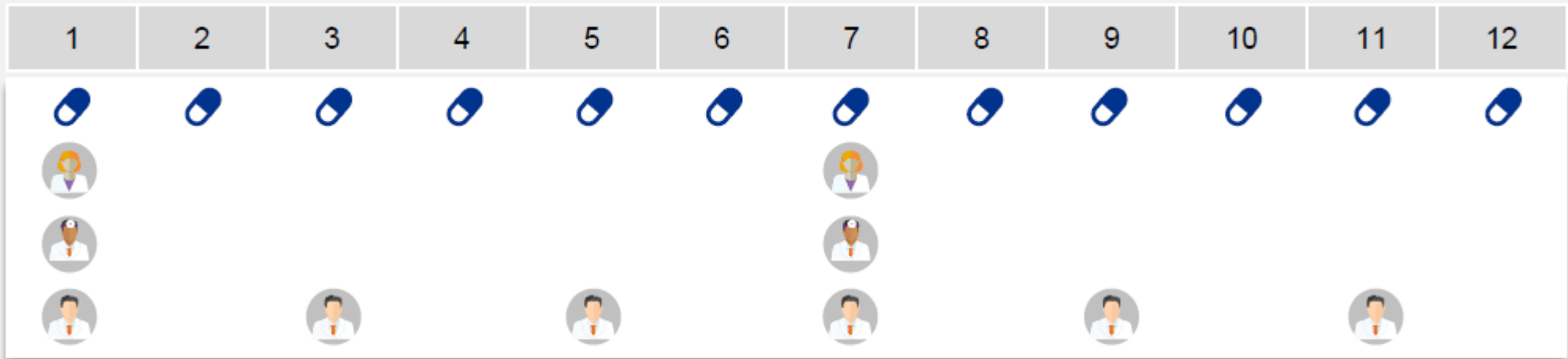




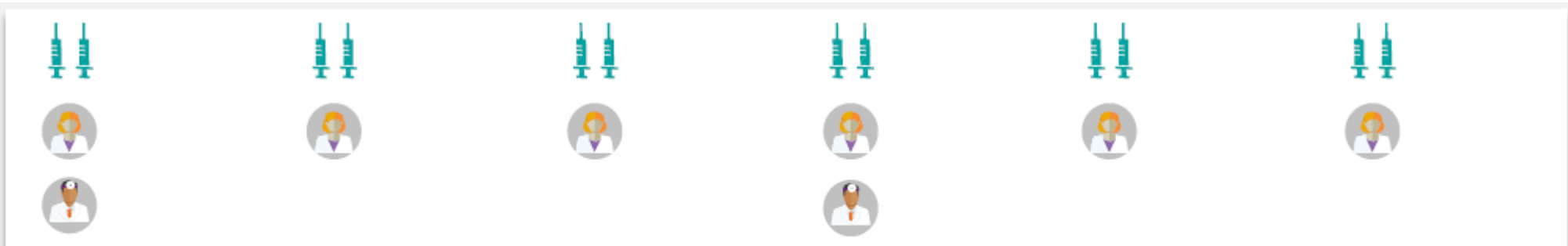
CARLA NEW delivery model in HIV

ORAL ARV
(CURRENT)

Month (maintenance phase only; oral lead-in not shown)



2 MONTHLY
LAR



Physician
consultation



Nurse visit



Hospital
pharmacy visit



Oral ARV
(current)

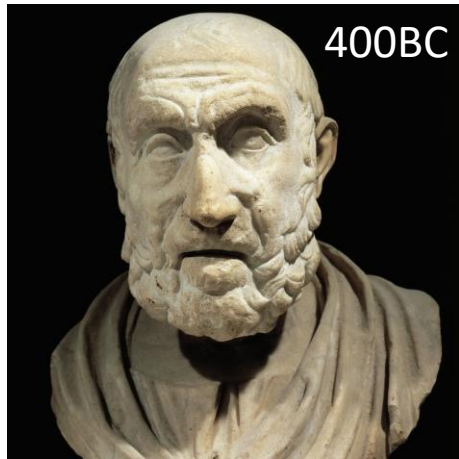


LAR 3mL
injections



1. **This new treatment paradigm will require changes to the current standard of care** of prescribing oral antiretroviral therapies including the logistics of delivering a complete antiretroviral treatment regimen as LA injectable therapy.
2. **This new treatment paradigm will require different requirements** such as more frequent visits by patients to see a provider and receive injections, as well as potentially require greater resources in the clinical setting to administer the injection.
3. **As this is a promising new treatment modality for people living with HIV (PLHIV), it is important to understand how to optimize the delivery of CAB + RPV LA** from a PLHIV, HCP and healthcare system perspective

Adherence, Retention, Completion: The ARC of benefit for long-acting drug delivery



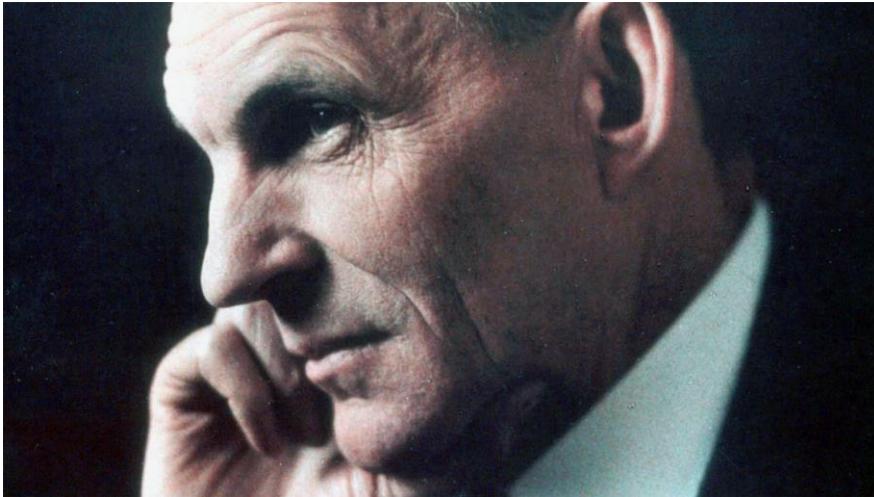
400BC

"Keep a watch also on the faults of the patients, which often make them lie about the taking of things prescribed"

"What they have done never results in a confession, but the blame is thrown upon the physician."

- Long-acting drug delivery has the potential to be transformative for patient management:
 - Issues of non-**adherence** are partially or entirely mitigated.
 - Problems with **retention** in therapy programmes are removed for some indications.
 - For indications within the range of the duration of exposure, **completion** may be achievable from a single visit.

grazie per l'attenzione



*“C'è vero progresso solo
quando i vantaggi di una
nuova tecnologia diventano
per tutti”*

Henry Ford