10° WORKSHOP NAZIONALE CISAI

MILANO

PREVENZIONE E GESTIONE DELLE CO-MORBIDITÀ ASSOCIATE ALL'INFEZIONE DA HIV

PRESIDENTI
PAOLO BONFANTI
ANTONIO DI BIAGIO

30 SETTEMBRE
1 OTTOBRE
2021

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FONDAZIONE ASIA

UniSR
Università Vita-Salute
San Raffaele

I.R.C.C.S. Ospedale
San Raffaele

Verso la terapia con i long-acting: cosa dobbiamo aspettarci?

Silvia Nozza
Ospedale San Raffaele, Milano

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Potenziale conflitto d'interessi da dichiarare

Tipo di affiliazione o supporto finanziario	Sponsor
GRANT	GILEAD
GRANT	ViiV Healthcare
EDUCATIONAL HONORARIA	MSD
EDUCATIONAL HONORARIA	Janssen-Cilag

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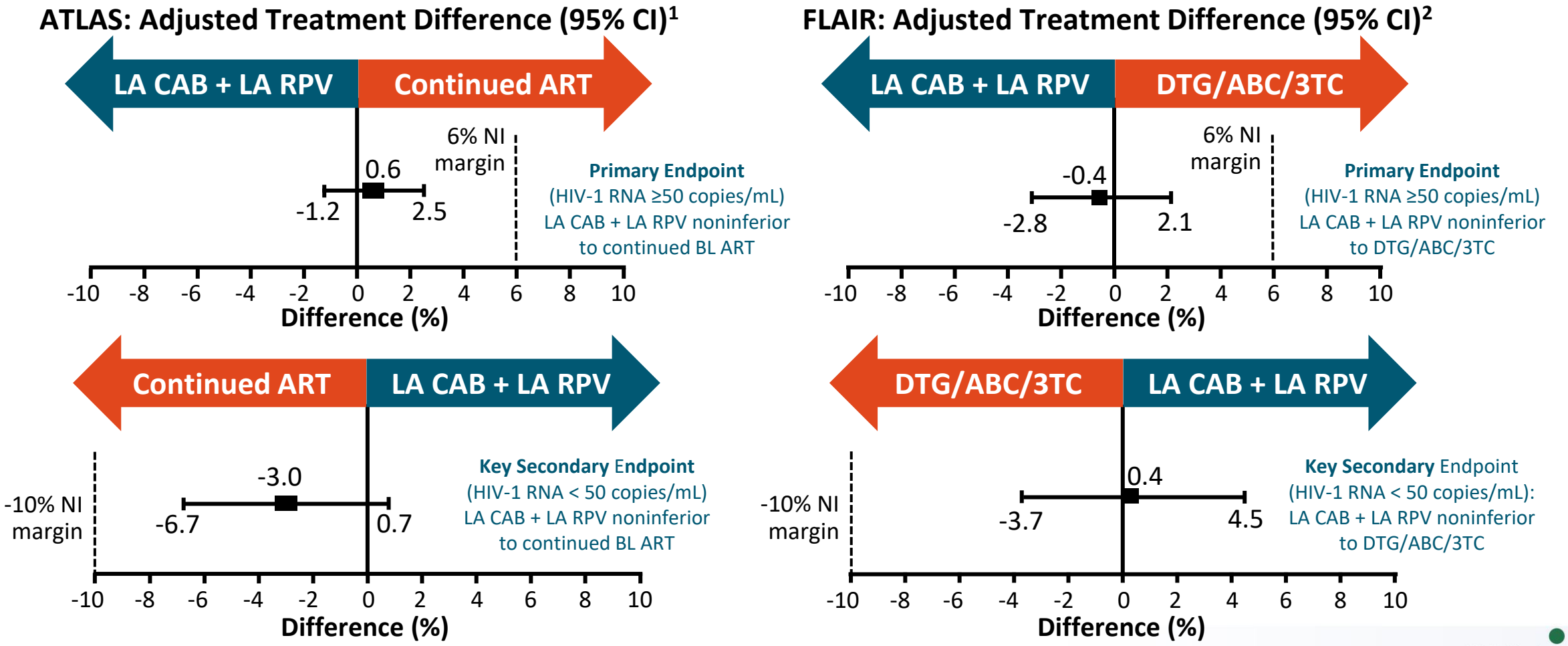
ATLAS and FLAIR: Long-Acting Intramuscular CAB + RPV After Initial Virologic Suppression With Oral Therapy



1. Swindells. NEJM. 2020;382:1112. 2. Orkin. NEJM. 2020;382:1124.

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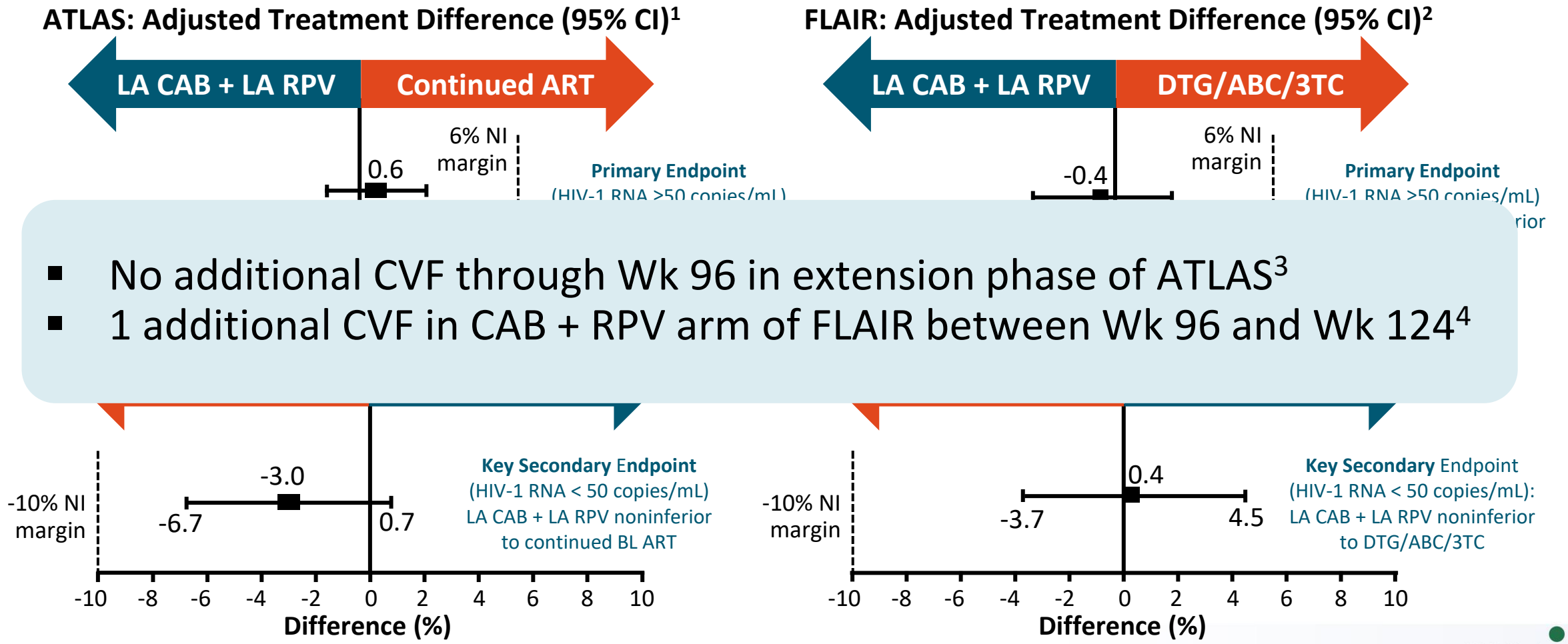
ATLAS and FLAIR: Wk 48 Virologic Outcomes With LA CAB + RPV



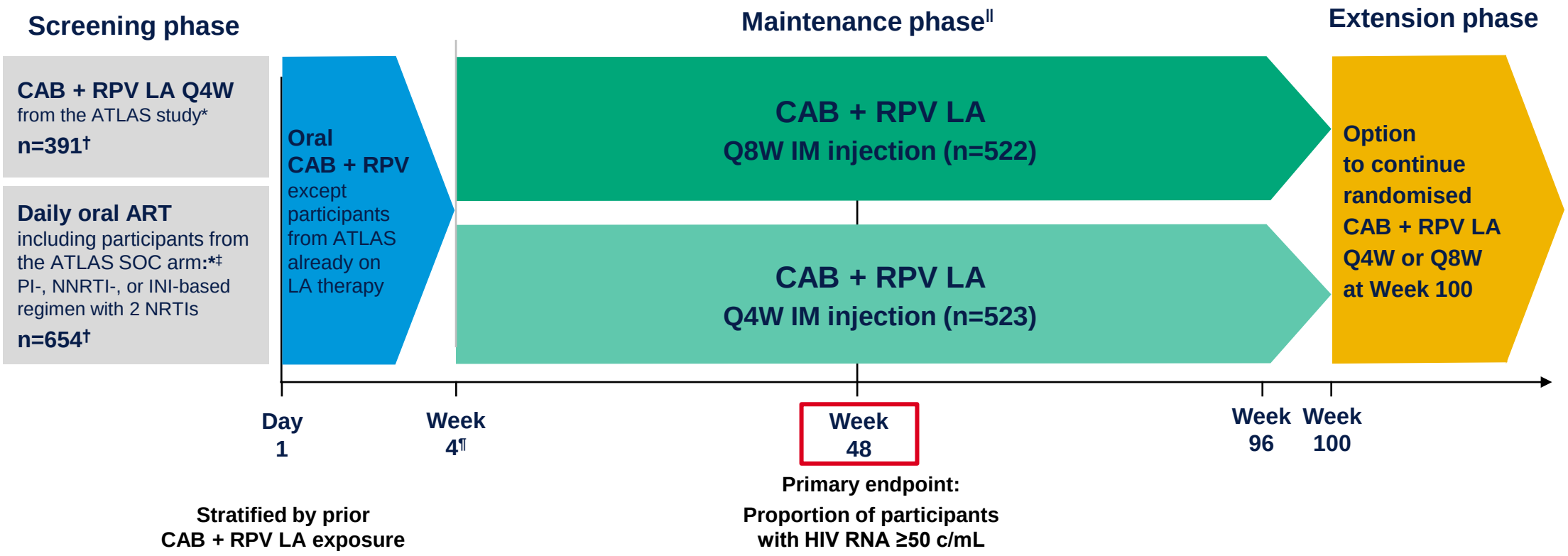
- No additional CVF through Wk 96 in extension phase of ATLAS[3]
- 1 additional CVF in CAB + RPV arm of FLAIR between Wk 96 and Wk 124[4]

1. Swindells. NEJM. 2020;382:1112. 2. Orkin. NEJM. 2020;382:1124.

Slide credit: clinicaloptions.com

ATLAS-2M: Study Design

Phase III, randomised, international, multicentre, open-label, non-inferiority design[1,2]

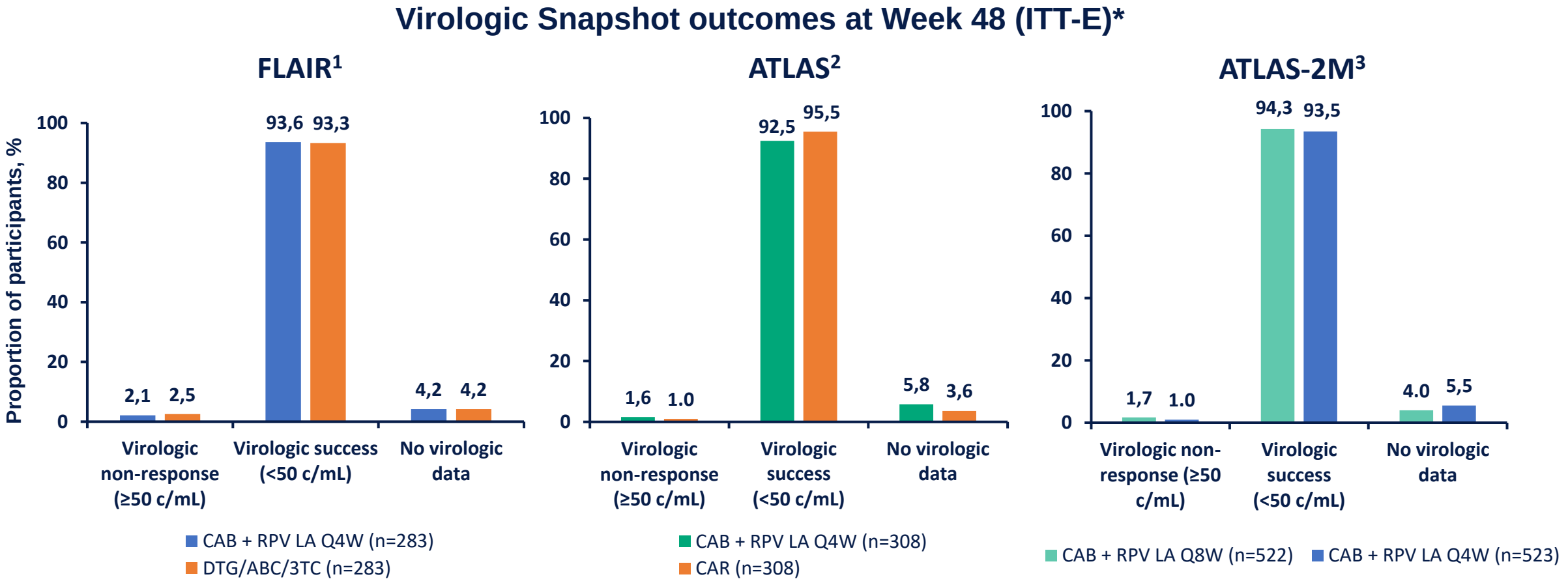


*Participants transitioning from ATLAS must have been on CAB + RPV LA Q4W or a current ART regimen through at least Week 52 of the ATLAS study and had plasma HIV-1 RNA <50 c/mL at screening; †ITT-E population; ‡SOC participants not transitioning from the ATLAS study were to be on uninterrupted current regimen (either the initial or second combined ART regimen) for at least 6 months prior to screening. Documented evidence of at least two plasma HIV-1 RNA measurements <50 c/mL in the 12 months prior to screening, one within the 6–12 month window and one within 6 months prior to screening, was required. Participants were excluded if they had a history of VF, evidence of viral resistance based on the presence of any resistance-associated major INI or NNRTI mutation (except K103N) from prior genotype assay results; §1,149 participants were screened, and 1,049 participants were randomised. Four participants did not receive study drug and therefore were not part of the ITT-E population; ‖Participants who withdraw from the IM regimen must go into 52-week long-term follow-up if randomised regimen is not yet locally approved and commercially available; ¶Participants on OLI treatment attended a Week 4 visit to assess tolerability. In participants in the Q4W arm who had an OLI, the first LA dose was CAB 600 mg + RPV 900 mg

NNRTI, non-nucleoside reverse transcriptase inhibitor; **OLI,** oral lead-in; **Q4W,** every 4 weeks; **Q8W,** every 8 weeks; **SOC,** standard of care

1. Overton ET, et al. Lancet 2021;396:1994–2005.
2. Overton ET, et al. CROI 2020. Oral 3334

CAB + RPV LA (Q4W or Q8W dosing) was Non-inferior to Continuing an Oral 3DR in Maintaining Virologic Suppression



CAB + RPV, the only complete long-acting HIV treatment, provides an alternative to daily oral dosing.
Oral daily regimens including a second NRTI did not demonstrate additional efficacy

*Primary endpoint: non-inferiority (HIV-1 RNA ≥50 c/mL) to comparator arm; key secondary endpoint: non-inferiority (HIV-1 RNA <50 c/mL) to comparator arm
3TC, lamivudine; **ABC,** abacavir; **CAR,** current antiretroviral regimen; **DTG,** dolutegravir; **ITT-E,** intent-to-treat-exposed

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. Lancet 2021;396:1994–2005

Risk Factors for Virologic Failure With LA CAB + RPV

- Post hoc analysis of Wk 48 phase III data[1]
  - ATLAS and FLAIR (Q4W dosing)
  - ATLAS-2M (Q4W and Q8W dosing)
- 13/1039 (1.25%) participants had CVF in ATLAS, FLAIR, ATLAS-2M
- Among 96.7% with 0 or 1 risk factor for CVF, 0.4% had CVF
- Q8W dosing was not a significant factor associated with CVF

Factors Associated With CVF	OR
RPV RAS(s) at baseline	40.36
Wk 8 RPV trough concentration	5.00
Baseline HIV-1 subtype A6/A1	5.92
BMI (kg/m^2) at baseline	1.13

No. of Baseline Factors Associated With CVF	CVF, %	HIV-1 RNA <50 c/mL, %
None	0.4	95
1	0.4	96
≥2	26	71
Total	**1.3**	**94**

--- INDICATIONS AND USAGE----------
CAB/RPV … is indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.[2]

DHHS note regarding HBV coinfection:
LA CAB + RPV not active against HBV[3]

1. Cutrell. AIDS. 2021;35:1333. 2. Injectable CAB+RBV prescribing information. January 2021.
3. DHHS Guidelines. June 2021.

Combination of Baseline RPV RAMs, Subtype A6/A1 and/or BMI ≥30 kg/m^2 Modestly Increased the Risk of CVF

Outcomes by presence of key baseline risk factors (RPV RAMs,* subtype A6/A1 and/or BMI ≥30 kg/m^2):[1]

Baseline factors	CVF, n (%)†	Virologic success, n (%)‡
None of the three baseline factors	3/732 (0.41)	694/732 (95)
Any one of the three baseline factors	1/272 (0.37)	261/272 (96)
Two or more of the three baseline factors	**9/35 (26)**	**25/35 (71)**
TOTAL [95% CI]	13/1,039 (1.3) [0.67, 2.13]	980/1,039 (94) [92.74, 95.65]

- Combination of two or more baseline factors was uncommon among study participants (3.4%; n=35/1,039)[1]
- CVF rate was very low (<0.5%) when only one or none of these baseline factors was present[1]
- CAB + RPV LA is indicated across a broad group of virologically suppressed patients, with additional clinical consideration in the small subgroup of patients with at least two BL factors[3,4]

No single BL factor significantly impacted the risk of VF with CAB + RPV LA; participants with ≥2 risk factors at BL were rare

*RPV RAMs were evaluated retrospectively from proviral DNA, and identified per the IAS-USA 2019 list of mutations[2]
†Defined as two consecutive measurements of HIV-1 RNA >200 c/mL
‡Based on the FDA Snapshot algorithm of HIV-1 RNA <50 c/mL
FDA, US Food and Drug Administration

1. Cutrell AG, et al. AIDS. 2021 [Online ahead of print] ;**2.** Wensing AM, et al. Top Antivir Med 2019;27:111–21
3. Vocabria. EU SmPC. March 2021; **4.** Rekambys. EU SmPC. January 2021

Switch Strategies for Virologically Suppressed Persons

- **Documented toxicity** caused by one or more of the antiretrovirals included in the regimen.
- **Prevention of long-term toxicity** (proactive switch). This may include person's concerns about safety
- **Avoidance of drug-drug interactions**.
- **Planned pregnancy or women wishing to conceive,** see Antiretroviral Drugs Not Recommended in Women who Wish to Conceive or Become Pregnant while on ART
- **Ageing and/or comorbidity** with a possible negative impact of drug(s) in current regimen, e.g. on CVD risk, metabolic parameters
- **Simplification**: to reduce pill burden, adjust food restrictions, improve adherence and reduce monitoring needs
- **Protection from HBV** infection or reactivation by including tenofovir in the regimen
- **Regimen fortification**: Increasing the barrier to resistance of a regimen in order to prevent VF (e.g. in persons with reduced adherence)
- **Cost reduction:** switching to the generic form of their current regimen, if available

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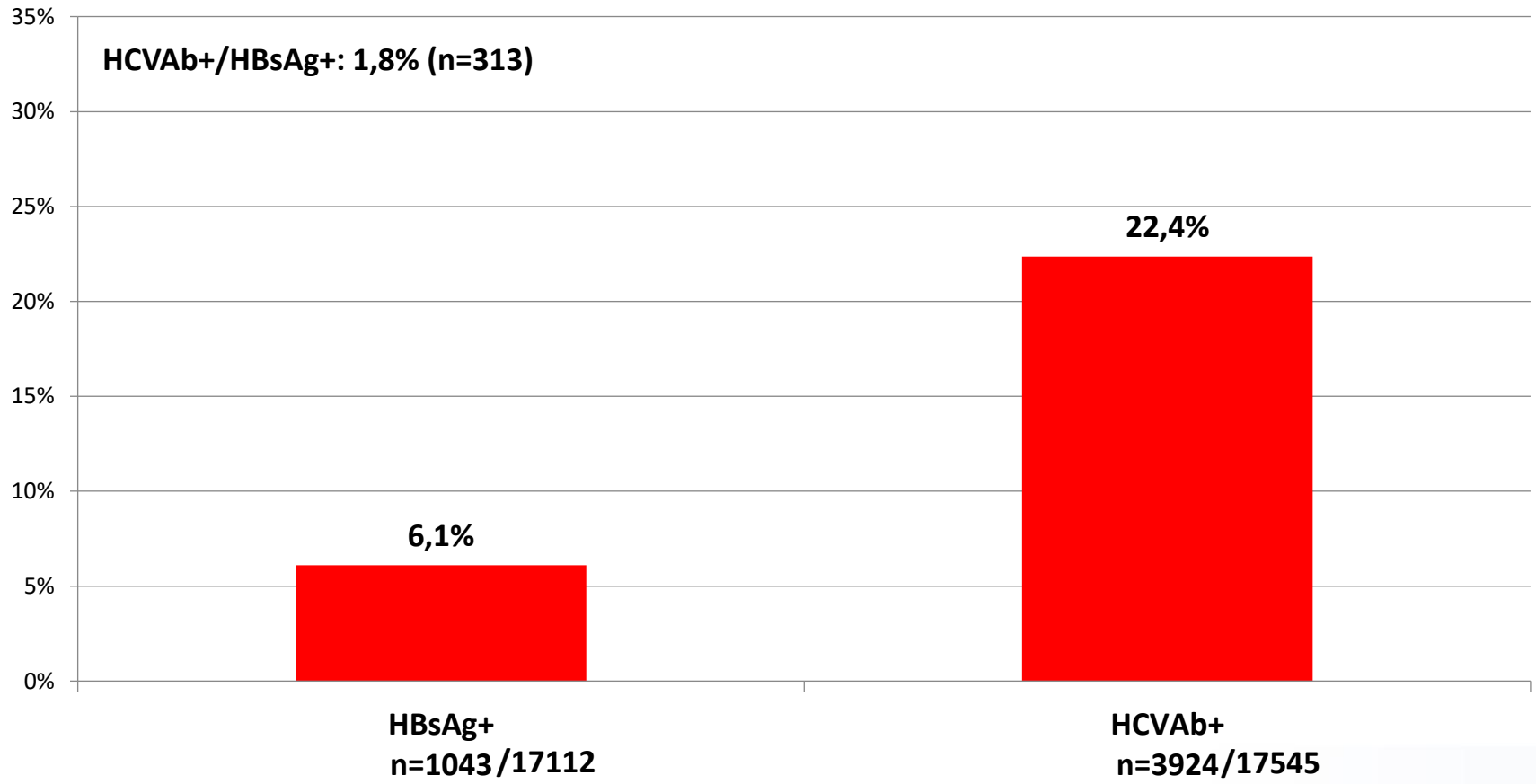
ITALIAN COHORT NAIVE ANTIRETROVIRALS

HBsAg and HCVAb positivity in ICONA patients



Jul 2021 Report

DHHS Guidelines: Practical Considerations for LA CAB + RPV

Administration

- **Recommended to be administered only by HCP**; important to coordinate efforts between clinical systems, pharmacies, patients
- Requires oral CAB + RVP lead-in dosing for ~1 mo to assess tolerability; initiate injections on last day of oral lead-in period
- Initiate injections with loading doses (CAB 600 mg/3 mL + RPV 900 mg/3 mL) followed by monthly continuation doses (CAB 400 mg/2 mL + RPV 600 mg/2 mL)
- 23-gauge, 1.5-inch intramuscular needle recommended (use 2-inch needle if BMI >30 kg/m^2)
- Give ventrogluteal IM injections on opposite sides when possible or ≥2 cm apart if given on same side

DHHS Guidelines. June 2021.

Slide credit: clinicaloptions.com

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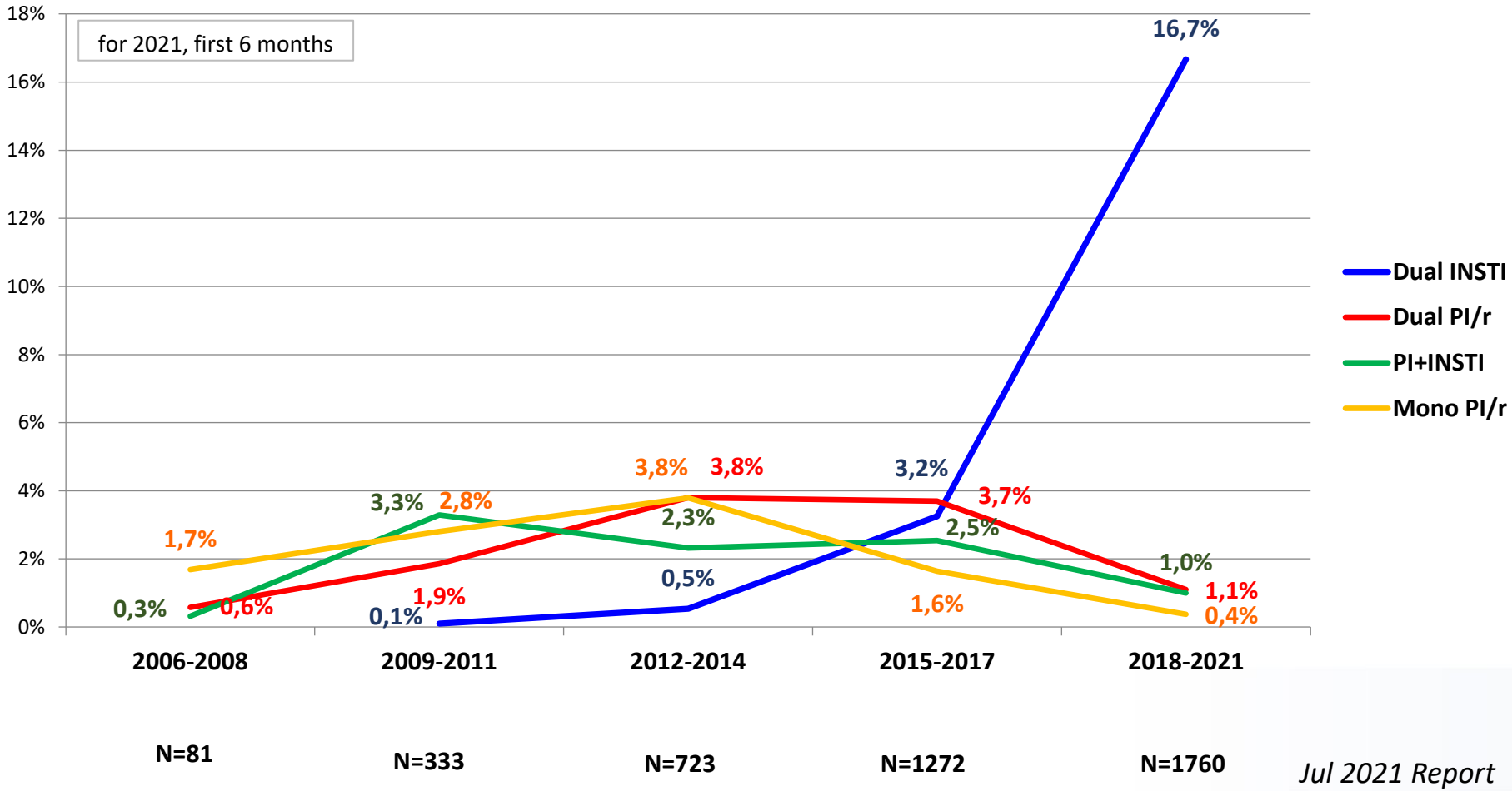
ITALIAN COHORT NAIVE ANTIRETROVIRALS

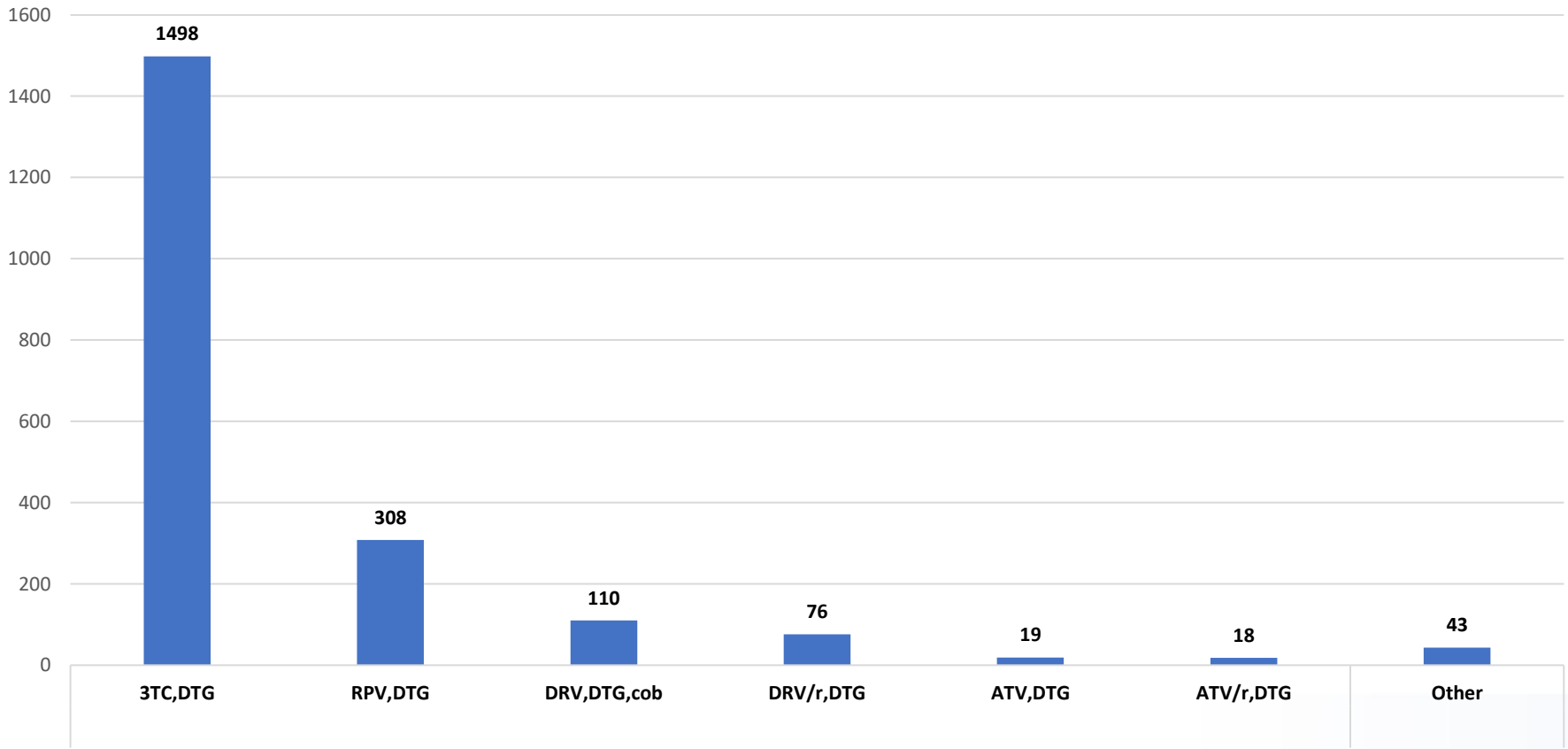
Proportion of mono/dual PI therapies (n=4169) according to calendar period of starting



Jul 2021 Report

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Most used DTG-containing mono/dual therapies



Jul 2021 Report

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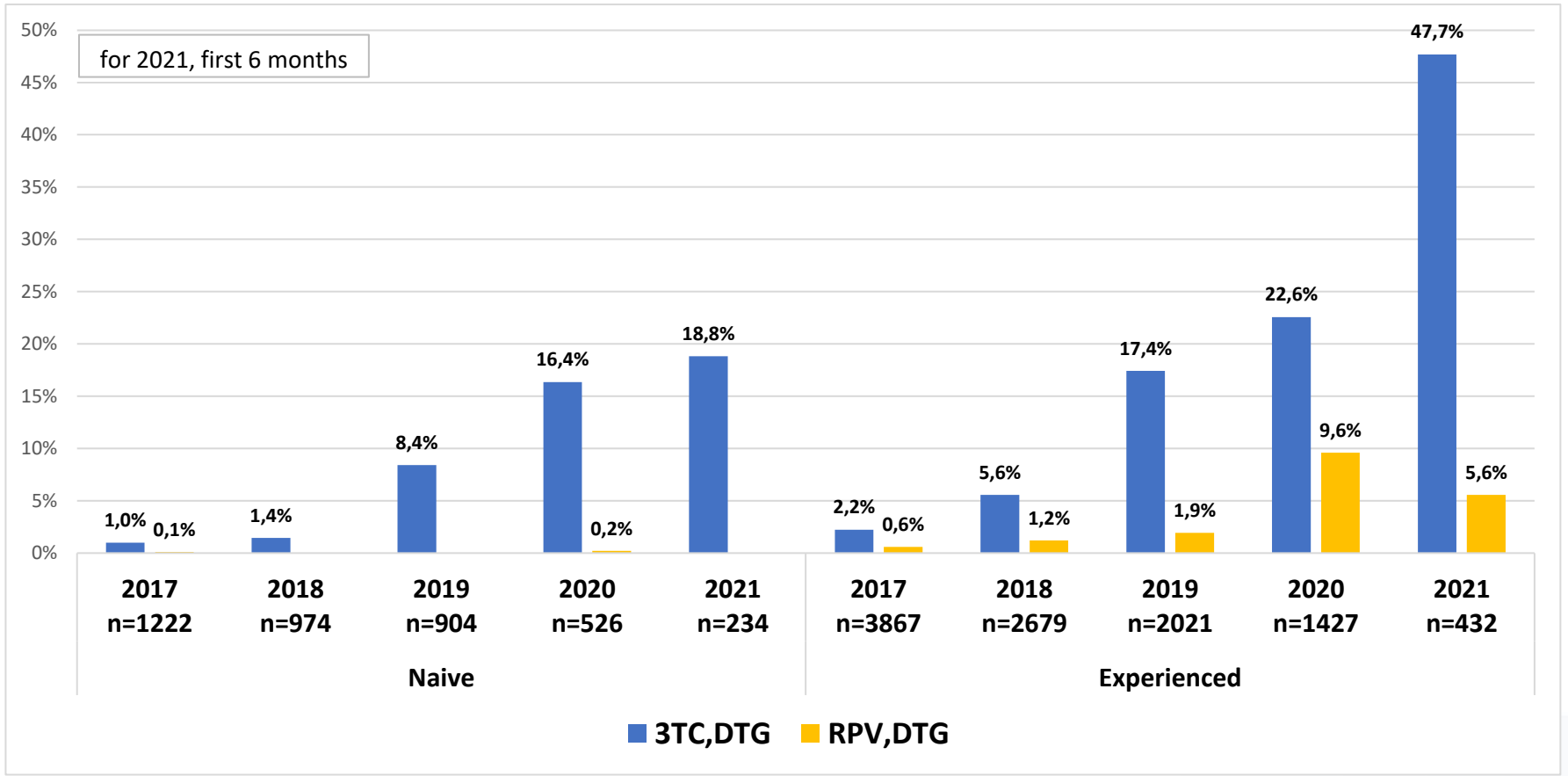
ITALIAN COHORT NAIVE ANTIRETROVIRALS

DTG+3TC and DTG+RPV dual therapies used in naïve and experienced patients from 2017 to 2021



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DHHS Guidelines: Practical Considerations for LA CAB + RPV

Monitoring and Missed Doses

- HIV-1 RNA: 4-8 wk after switch to LA CAB + RPV and after unplanned missed visits/delayed dosing
- If viremia develops, test for resistance (including INSTI resistance)
- Oral-bridging therapy should be made available for planned missed doses
- If <2 mo since last injections, resume prior continuation dosing schedule
- If >2 mo since last injections, administer loading dose, followed by monthly continuation dosing
- When stopping, transition to suppressive oral regimen within 4 wk of last IM doses

DHHS Guidelines. June 2021.

Slide credit: clinicaloptions.com

Lazarus et al. BMC Medicine (2016) 14:94
DOI 10.1186/s12916-016-0640-4

BMC Medicine

OPINION Open Access

Beyond viral suppression of HIV – the new quality of life frontier

Jeffrey V. Lazarus[1,2*], Kelly Safreed-Harmon[2], Simon E. Barton[3], Dominique Costagliola[4], Nikos Dedes[5], Julia del Amo Valero[6], Jose M. Gatell[7], Ricardo Baptista-Leite[8,9], Luís Mendão[5], Kholoud Porter[10], Stefano Vella[11] and Jürgen Kurt Rockstroh[12]

Contents available at PubMed
www.aidsreviews.com

PERMANYER

AIDS Rev. 2019;21:135-142

"Moving Fourth": A Vision Toward Achieving Healthy Living with HIV Beyond Viral Suppression

Giovanni Guaraldi[1], Joop Arends[2], Thomas Buhk[3], Mario Cascio[4], Adrian Curran[5], Eugenio Teofilo[6], Guido Van Den Berk[7] and Christian Verger[8]*

SERIES | HIV OUTCOMES BEYOND VIRAL SUPPRESSION | VOLUME 6, ISSUE 12, E869-E877, DECEMBER 01, 2019

Reorienting health systems to care for people with HIV beyond viral suppression

Kelly Safreed-Harmon, MS • Jane Anderson, MD • Natasha Azzopardi-Muscat, PhD • Georg M N Behrens, MD • Prof Antonella d'Arminio Monforte, MD • Udi Davidovich, MD • et al. Show all authors

Published: November 24, 2019 • DOI: https://doi.org/10.1016/S2352-3018(19)30334-0 • Check for updates

nature COMMUNICATIONS

NATURE COMMUNICATIONS | (2021) 12:4450

PERSPECTIVE

https://doi.org/10.1038/s41467-021-24673-w OPEN

Check for updates

Consensus statement on the role of health systems in advancing the long-term well-being of people living with HIV

Jeffrey V. Lazarus[1✉], Kelly Safreed-Harmon[1], Adeeba Kamarulzaman[2,3],

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CUSTOMIZE: Implementation of LA CAB + RPV

- Phase IIIb implementation-effectiveness study of LA CAB + RPV
  - Data collected July 2019 to October 2020 from 26 providers (physicians, injectors, admin) and 109 patients from 8 clinics

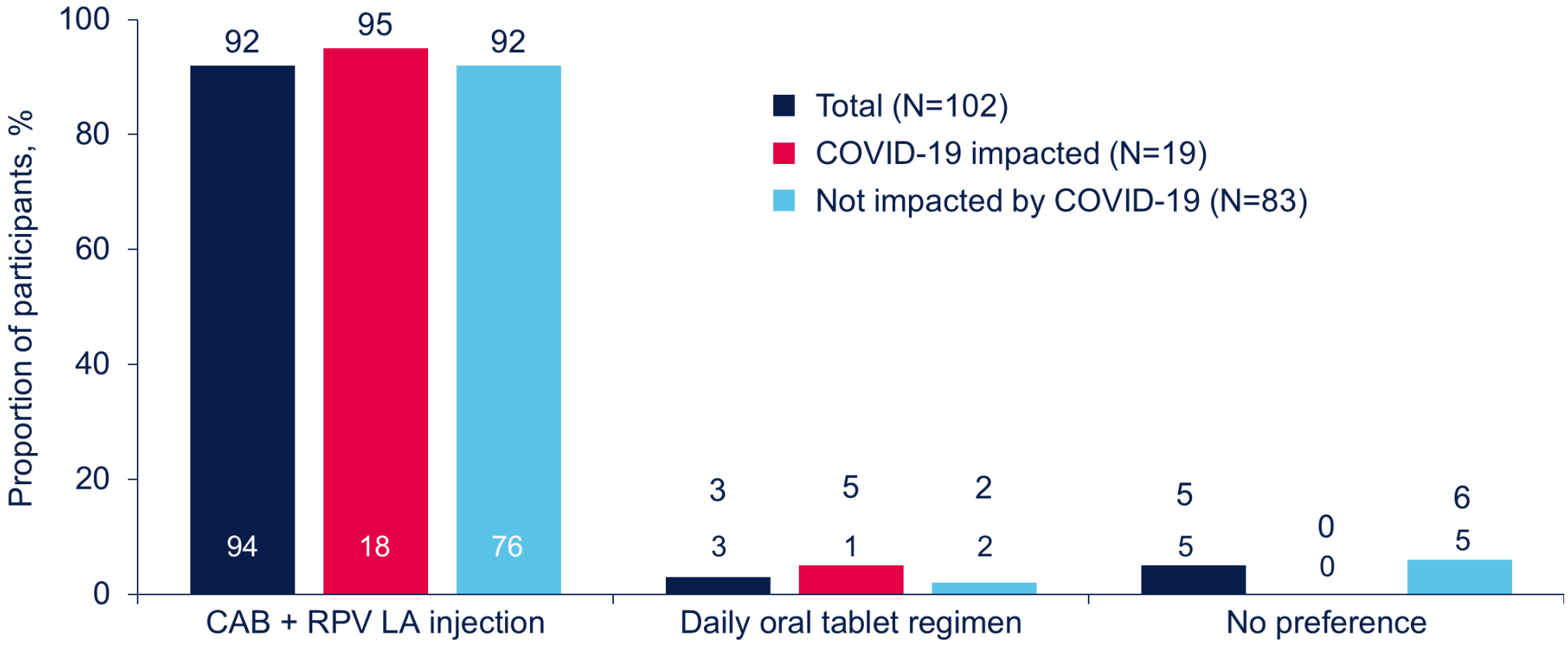
Virologic Outcome at Mo 12, n (%)	Patients (N = 115)
Virologic success (<50 copies/mL)	101 (88)
Virologic nonresponse (≥50 copies/mL)	0
No virologic data	14 (12)
▪ Discontinued due to AE or death	5 (4)*
▪ Discontinued for other reasons	8 (7)
▪ On study but missing data in window	1 (1)†
Scheduling injection visits	2

- Key strategies for successful **clinic implementation**
  - Good staff communication
  - Teamwork
  - Use of a web-based treatment planner
- Key implementation strategies for **patient adherence**
  - Good communication about dosing window
  - Effective appointment reminder systems
  - Designated staff for appointment tracking
- Duration of **visit length decreased** over time
  - Mo 1: median 57 min
  - Mo 11: median 34 min

Czarnogorski. IAS 2021. Abstr OAD0705.

Slide credit: clinicaloptions.com

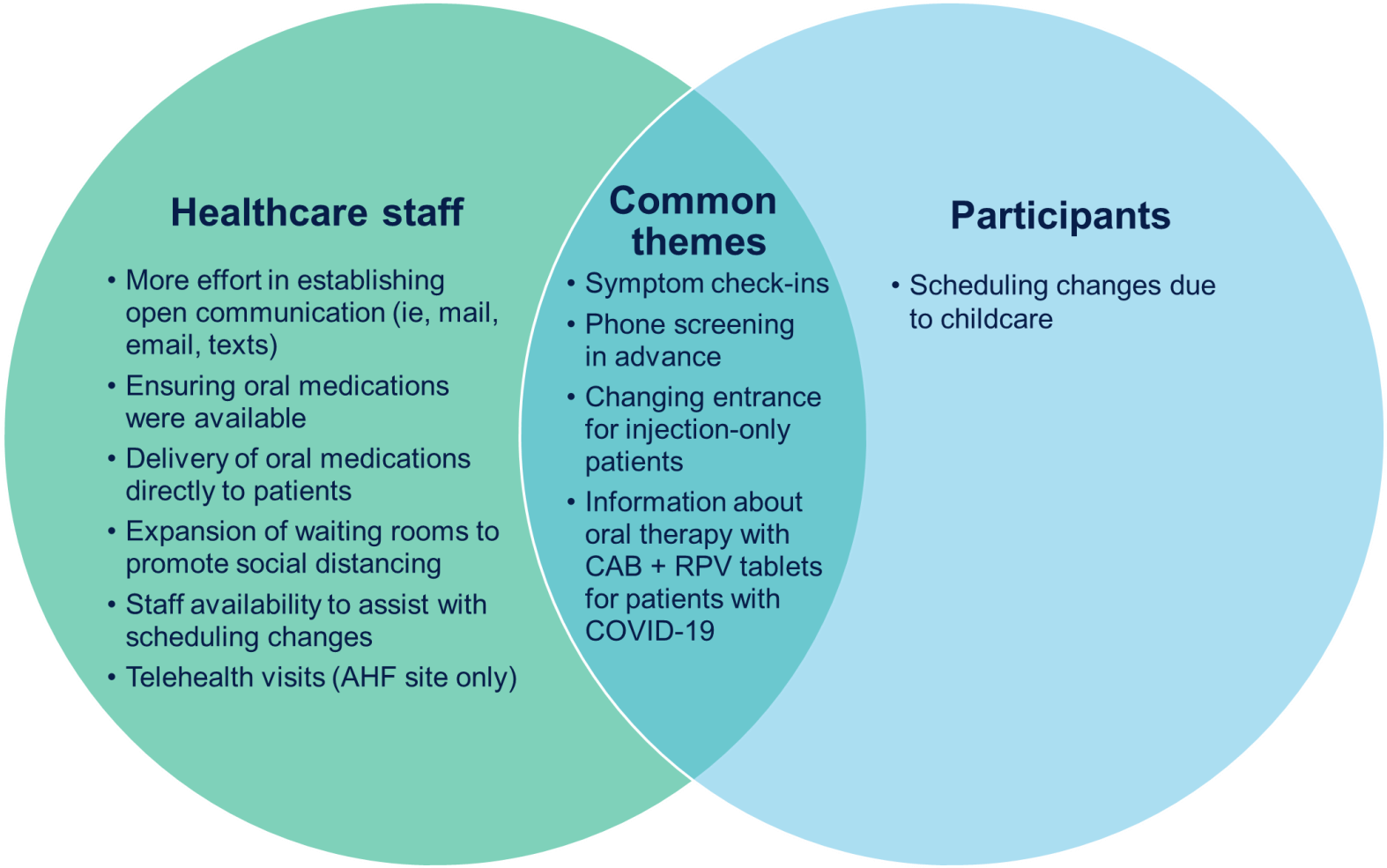
Participant HIV-1 Treatment Preference at Month 12 by COVID-19 Impact Status



Czarnogorski et al. IAS 2021; Virtual. Poster PED463.

Changes Made During the COVID-19 Pandemic

- During interviews at Month 12, healthcare staff and participants described multiple changes made in the clinic to facilitate CAB + RPV LA implementation during the COVID-19 pandemic



- AHF, AIDS Healthcare Foundation.

Czarnogorski et al. IAS 2021; Virtual. Poster PED463.

Conclusions

- During the COVID-19 pandemic, CAB + RPV LA implementation remained highly acceptable and appropriate among healthcare staff and participants in CUSTOMIZE
- 8 participants were given temporary oral therapy for missed injection visits and maintained uninterrupted ART, all of whom restarted LA therapy without virologic failure
- Acceptability of attending monthly clinic visits, preference for LA ART, and treatment effectiveness remained high among participants, including the 19 participants with COVID-19–impacted visits
- Despite healthcare disruptions caused by the COVID-19 pandemic, implementation data from CUSTOMIZE suggest that CAB + RPV LA is an appealing treatment option from the perspective of both healthcare providers and PLHIV

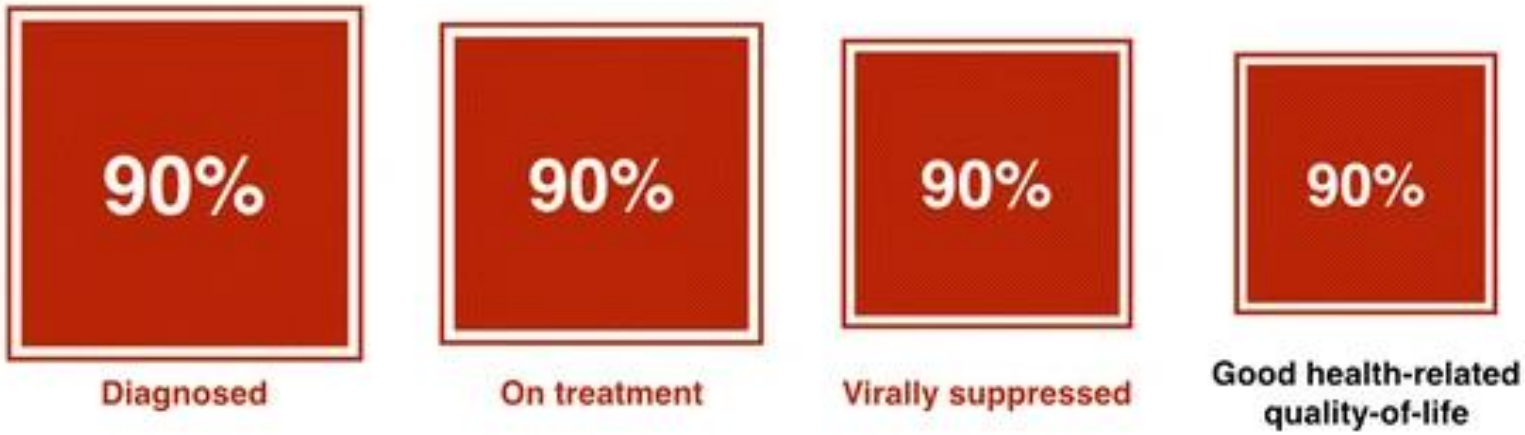
Czarnogorski et al. IAS 2021; Virtual. Poster PED463.

Beyond viral suppression of HIV - the new quality of life frontier[1]

In 2016, the **World Health Organization (WHO)** adopted a new Global Health Sector Strategy on HIV for 2016–2021.
It establishes 15 ambitious targets, including the '**90-90-90**' target calling on health systems to reduce under-diagnosis of HIV, treat a greater number of those diagnosed, and ensure that those being treated achieve viral suppression.

However, what about the millions of people already living with HIV?

What next following viral suppression?



*Adapted from: UNAIDS. 90-90-90: an ambitious treatment target to help end the AIDS epidemic. 2014. Available at http://unaids.org/sites/default/files/media_asset/90-90-90_en_0.pdf. Accessed on 25 April 2016

The WHO strategy calls for person-centered chronic care for people living with HIV (PLHIV), implicitly acknowledging that viral suppression is not the ultimate goal of treatment. However, it stops short of providing an explicit target for health-related quality of life.

1. Lazarus et al. BMC Medicine (2016) 14:94

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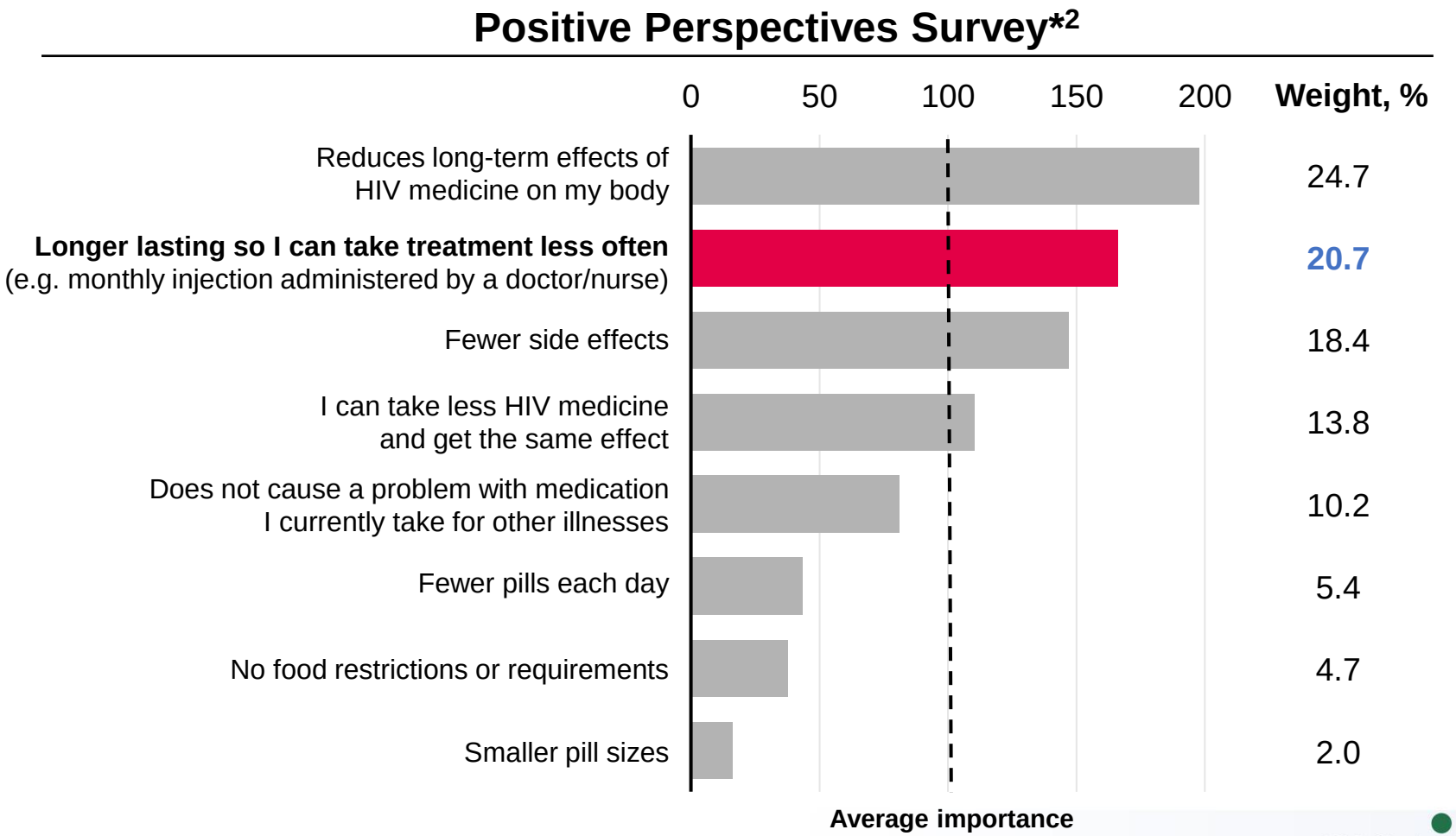
Patient surveys have identified long-lasting treatment, requiring less frequent dosing, as a priority for PLWHIV

- Treatments need to fit in with an individual patient's routine, expectations, and preferences[1]
- 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 burden[2]

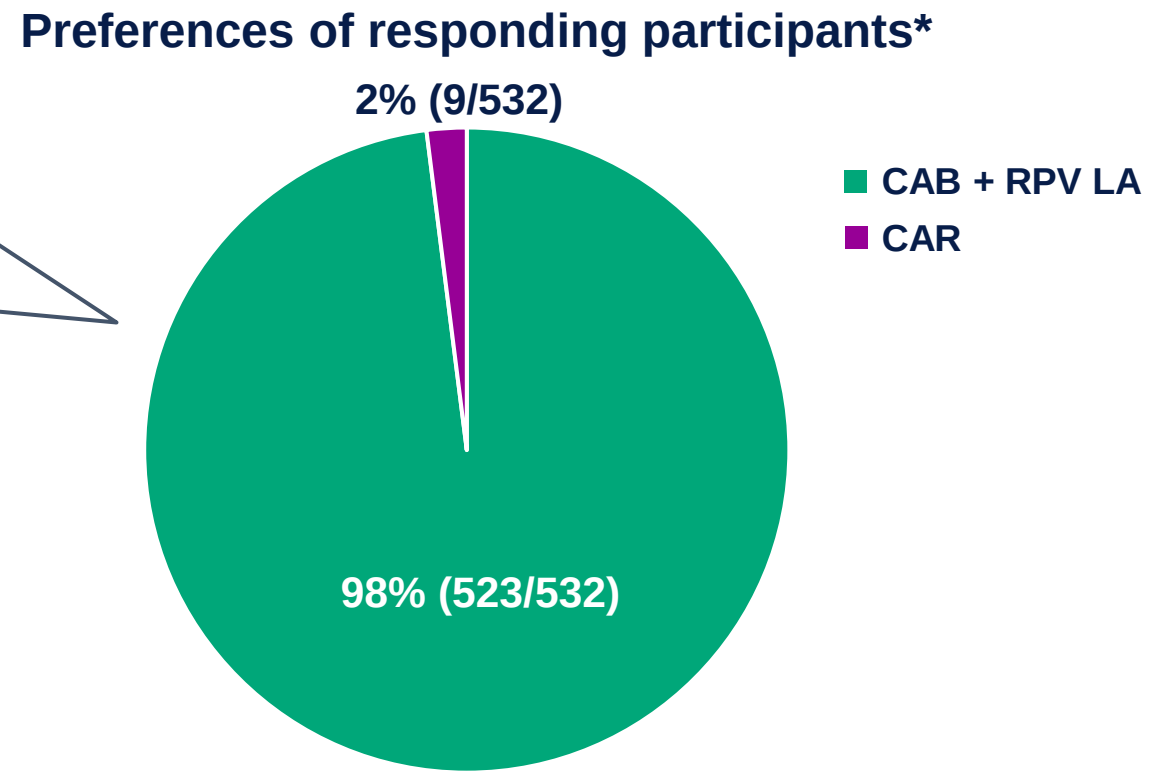


*The Positive Perspectives Survey was conducted between 2016 and 2017 in nine countries. Participants were enrolled from North America, Europe, and Australia (N=1,111)

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

Pooled ATLAS and FLAIR: CAB + RPV LA was Preferred Over Daily Oral ART

"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 prior to entering the study. ***Which therapy do you prefer?****"*



98% of responding participants from ATLAS + FLAIR preferred CAB + RPV LA over CAR at Week 48

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

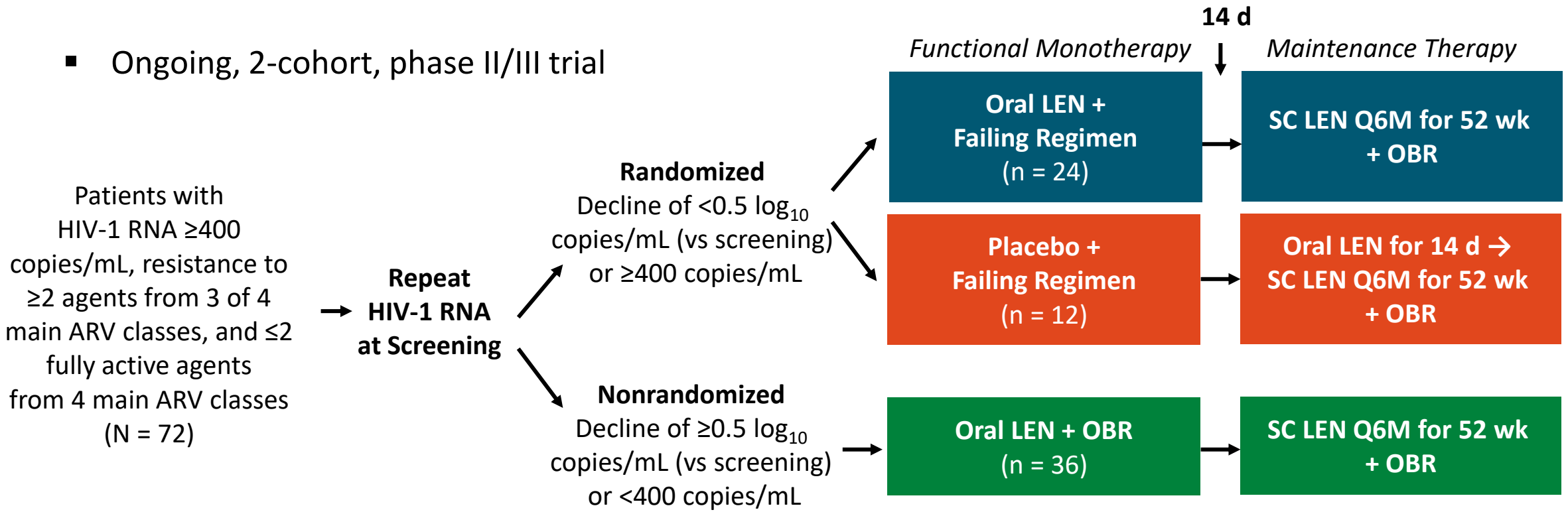
CAPELLA: Background

- Lenacapavir: HIV capsid inhibitor that prevents nuclear assembly, virus assembly and release, and capsid assembly[1,2]
  - Novel MOA may be of benefit in heavily treatment-experienced patients with MDR HIV-1
  - Retains full activity against NRTI-, NNTRI-, PI-, and INSTI-resistant HIV-1 in vitro[3-5]
  - Oral and SC formulations in development
- CAPELLA: ongoing, 2-cohort (randomized and nonrandomized), phase II/III trial evaluating the efficacy and safety of lenacapavir in heavily treatment-experienced patients
  - Primary endpoint achieved in randomized cohort when added as functional monotherapy to a failing ARV regimen: ≥0.5-log decline in HIV-1 RNA 88% with lenacapavir vs 17% with placebo at Day 14 (P <.0001)[6]
- Current report presents updated results from CAPELLA through Week 26[7]
  - Efficacy presented for randomized cohort; safety presented for randomized and nonrandomized cohorts

1. Link. Nature. 2020;584:614. 2. Bester. Science. 2020;370:360. 3. Yant. CROI 2019. Abstr 480. 4. Margot. CROI 2020. Abstr 529.
5. VanderVeen. CROI 2021. Abstr 128. 6. Segal-Maurer. CROI 2021. Abstr 127. 7. Molina. IAS 2021. Abstr OALX01LB02.

CAPELLA: Study Design

- Ongoing, 2-cohort, phase II/III trial



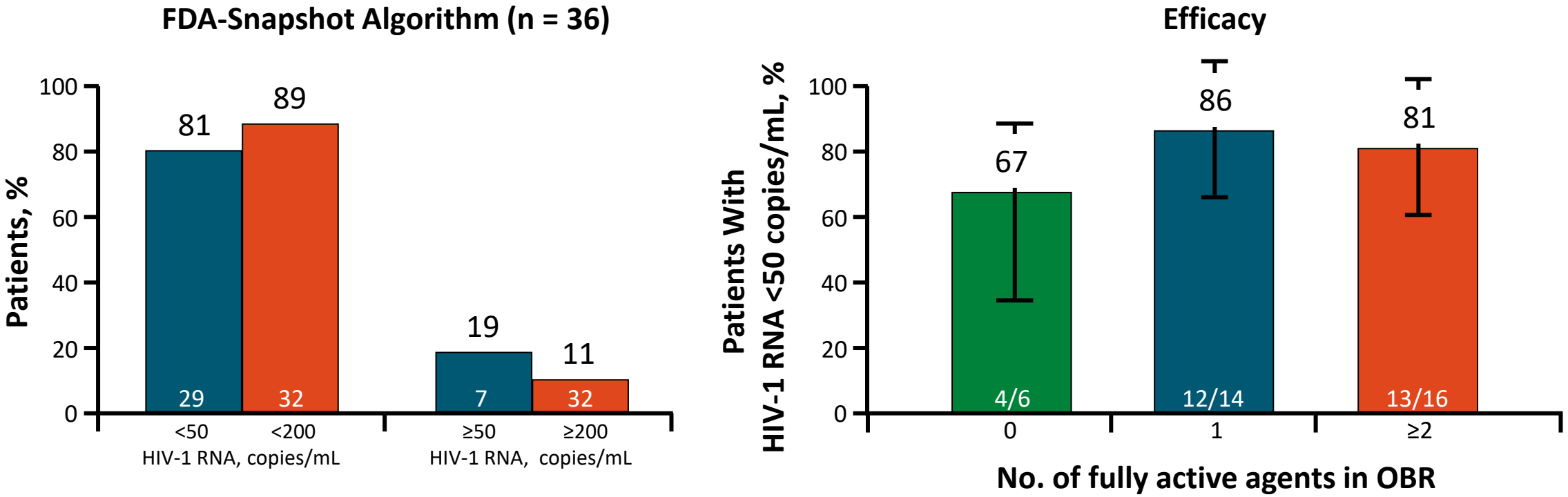
Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8; SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15 and Q6M thereafter.

- Primary endpoint achieved in prior analysis: ≥0.5 $\log_{10}$ copies/mL decline in HIV-1 RNA at Day 14 in randomized cohort
- Secondary endpoints: HIV-1 RNA <50 copies/mL, <200 copies/mL at Week 26 in randomized cohort

Slide credit: clinicaloptions.com

Molina. IAS 2021. Abstr OALX01LB02.

CAPELLA Secondary Endpoints: LEN Efficacy at Week 26 in Randomized Cohort



- Mean change in CD4+ cell count: +81 cells/mm^3
- Incidence of very low CD4+ cell count (<50 cells/mm^3) decreased from 22% (8/36) at baseline to 0% (0/34) at Week 26

Molina. IAS 2021. Abstr OALX01LB02. Reproduced with permission.

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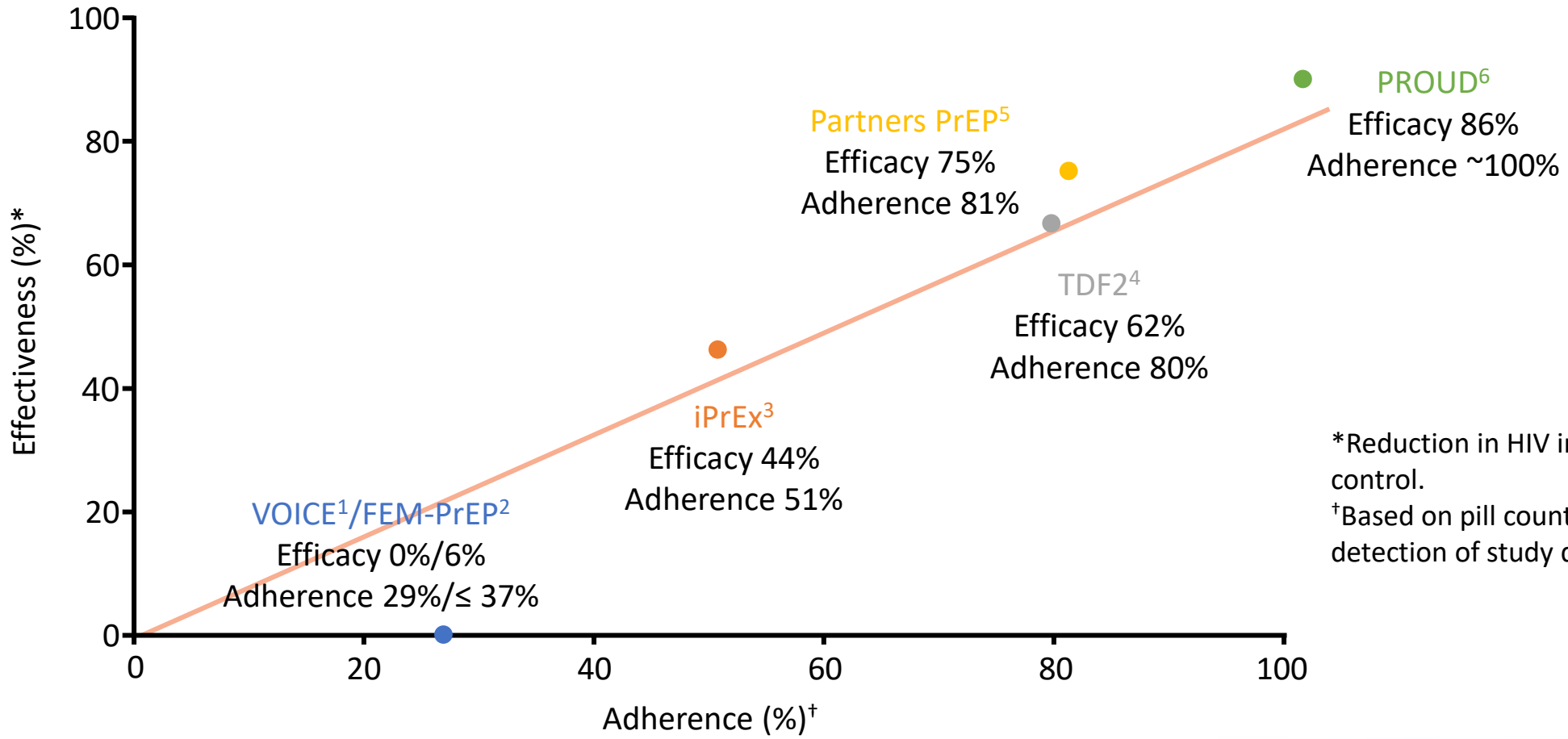
Select Daily Oral FTC/TDF PrEP Trials: Effectiveness Improves With Adherence

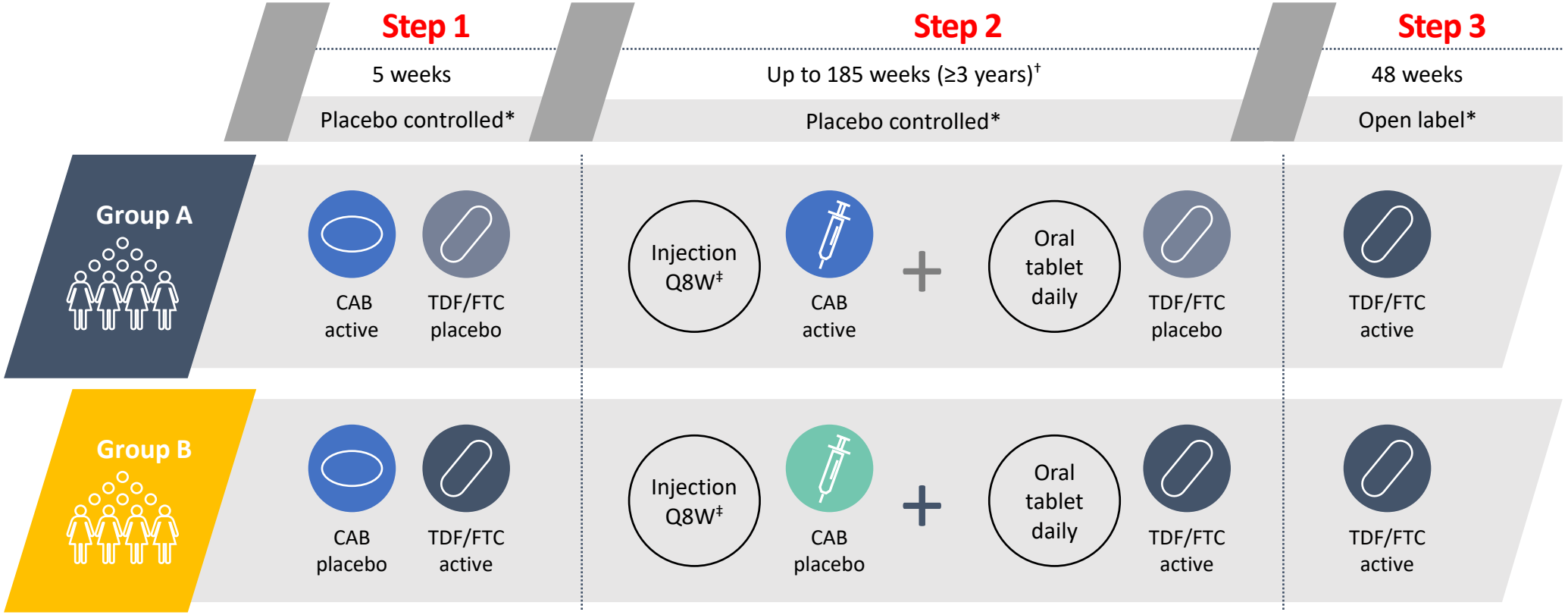


*Reduction in HIV incidence vs control.
†Based on pill counts or the detection of study drug in plasma.

1. Marrazzo. NEJM. 2015;372:509. 2. Van Damme. NEJM. 2012;367:411. 3. Grant. NEJM. 2010;363:2587.
4. Thigpen. NEJM. 2012;367:423. 5. Baeten. NEJM. 2012;367:399. 6. McCormack. Lancet. 2016;387:53.

HPTN 083 and HPTN 084: Study design

Studies to evaluate the safety and efficacy of CAB LA Q8W versus daily oral TDF/FTC for PrEP in HIV-uninfected MSM/TGW[1] or women[2]

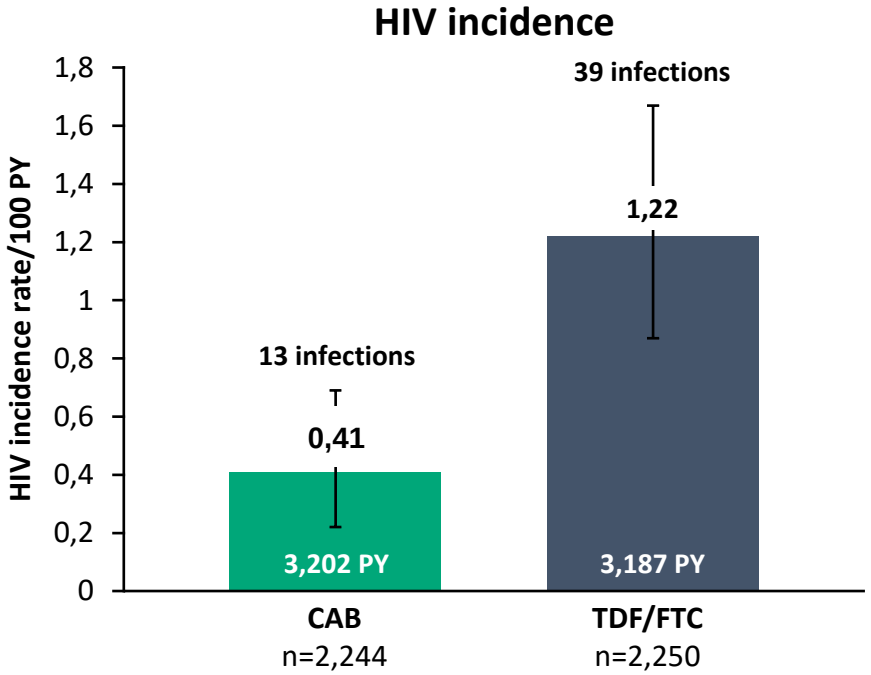


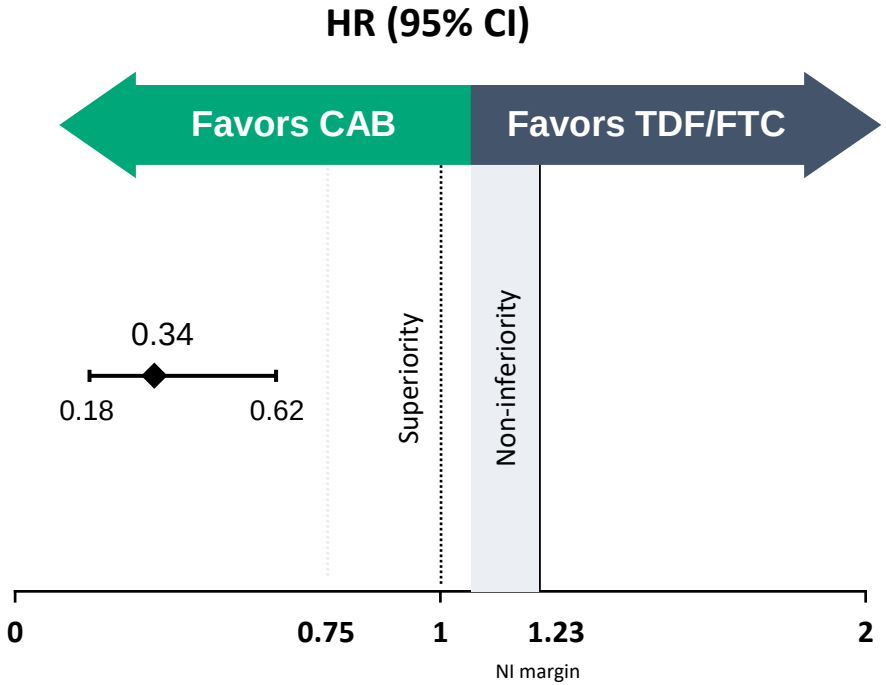
*In Steps 1 and 2, the tablets and injections will look alike, so staff and participants will not know if they are getting the active or placebo products. In Step 3, all participants will be given active TDF/FTC

†3 years for HPTN 083 and 3.5 years for HPTN 084

‡In Step 2, the first 2 injections are 4 weeks apart and 8 weeks apart thereafter

HPTN 083: Lower incidence of HIV infections with CAB than with TDF/FTC





- 52 HIV infections in 6,389 PY of follow-up
- 1.4 (IQR: 0.8–1.9) years median per-participant follow-up
- Pooled incidence 0.81 (95% CI: 0.61, 1.07) per 100 PY

CAB LA Q8W demonstrated superiority to TDF/FTC in preventing HIV infections in MSM and TGW at risk

HR, hazard ratio; NI, non-inferiority margin

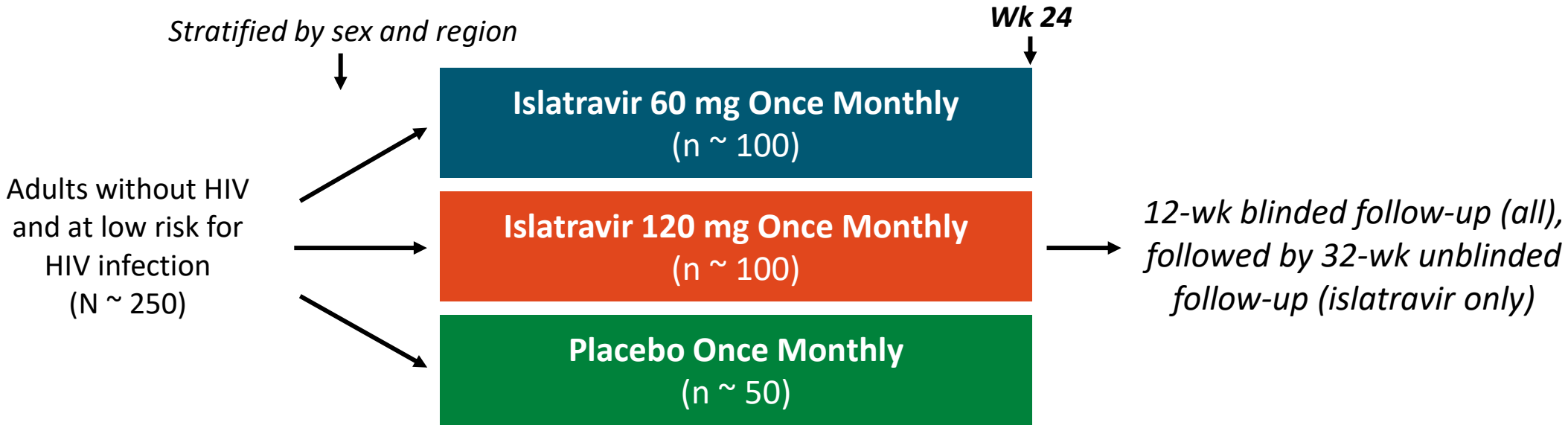
HPTN 084: HIV Incidence (Primary Endpoint)

Characteristic	CAB (n = 1614)	TDF/FTC (n = 1610)	Pooled (n = 3224)
HIV infections, n	4	36	40
Person-yrs	1953	1939	3892
HIV incidence per 100 person-yrs (95% CI)	0.2 (0.06-0.52)	1.86 (1.30-2.57)	1.03 (0.73-1.4)

- 89% lower risk of HIV infection for women in CAB group vs TDF/FTC group (*P* = .000027)
- 4 incident HIV infections in CAB arm
  - 2 observed despite CAB injections
  - 2 observed in the absence of CAB exposure

Islatravir for PrEP: Study Design

- Double-blind, randomized, placebo-controlled multicenter phase IIIa study
  - Current interim analysis includes 192 (76.8%) of planned 250 enrollees



- Primary outcomes: safety/tolerability, pharmacokinetics; exploratory outcomes: PBMC pharmacokinetics, tissue pharmacokinetics, hormonal DDIs

Hillier. HIVR4P 2021. Abstr OA04-05LB.

Islatravir for PrEP: Conclusions

- Islatravir administered once monthly achieved prespecified PrEP PK threshold established for efficacy in interim analysis[1]
- Islatravir was generally well tolerated with no reported serious adverse events[1]
- Enrollment in this phase IIa study completed November 24, 2020, with further results expected later in 2021[1]
- Islatravir for PrEP will be studied in 2 phase III studies
  - IMPOWER-022: Islatravir vs FTC/TDF in cisgender women at high risk of HIV infection[2]
  - IMPOWER-024: Islatravir vs FTC/TDF or FTC/TAF in men and transgender women who have sex with men at high risk of HIV infection[3]

1. Hillier. HIVR4P 2021. Abstr OA04-05LB. 2. NCT04644029. 3. NCT04652700.

Cosa dobbiamo aspettarci?

- Utilizzo della dual therapy CAB+RPV in PLWHIV con HIVRNA<50 copie/mL, senza coinfezione HBV e senza pregresse mutazioni. È sostenibile?

- Utilizzo di lenacapavir in PLWHIV MDR.

- PrEP per persone a rischio senza coinfezione HBV.