# HIV update 2022: quali nuove sfide ci attendono per vincere la guerra? Presente e futuro delle strategie di trattamento

Antonio Di Biagio

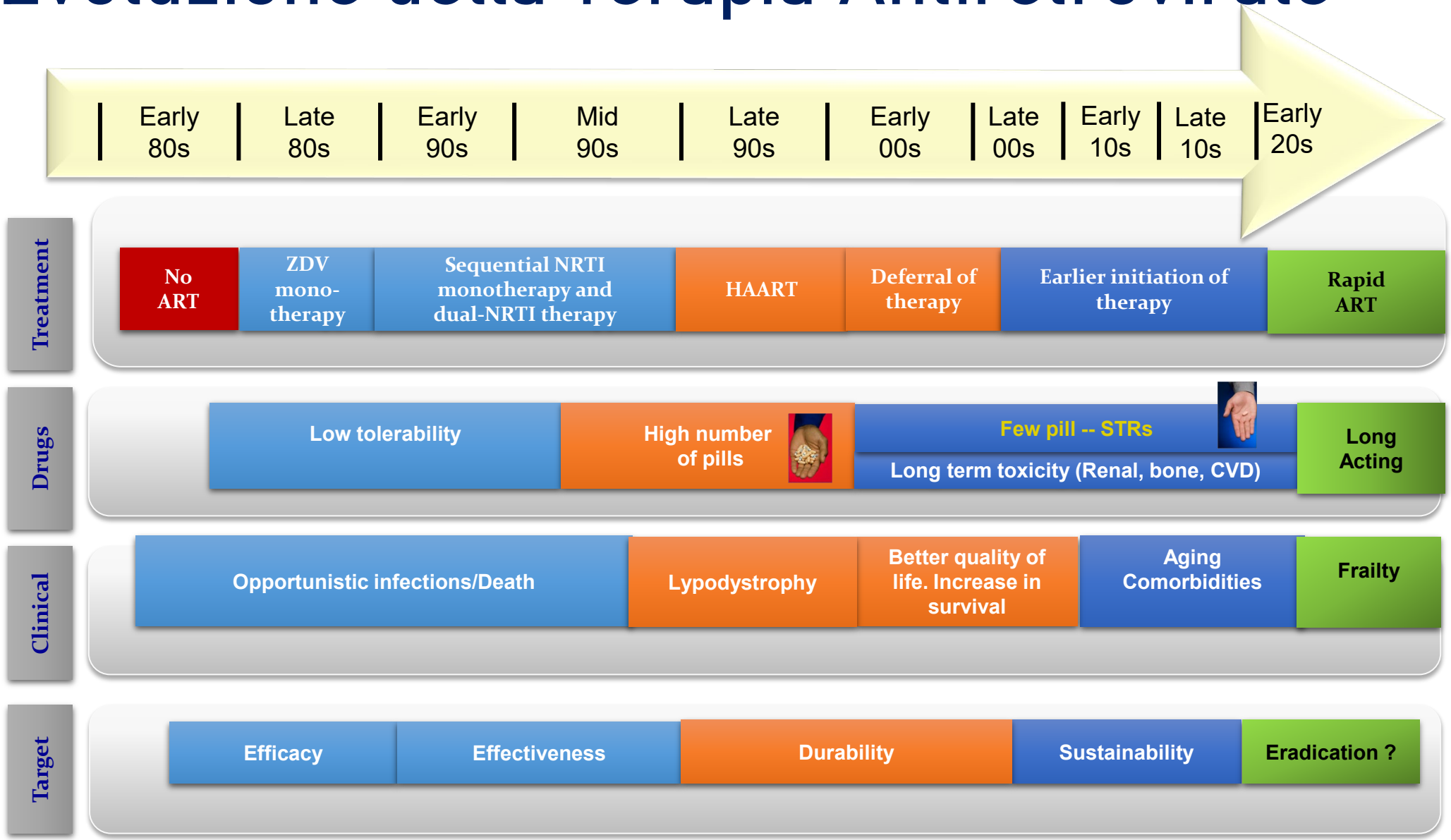
# Disclosures

- **I have participated in Advisory boards for ViiV Healthcare, Gilead Sciences, Janssen Cilag, Abbvie, MSD.**
- **I have received research grants from ViiV Healthcare and Gilead Sciences**
- **Member of the writing committee of the Italian HIV guidelines (SIMIT)**
- **Member of the ICAR scientific secretariat**

# 2022 update: quali argomenti ?

- **La prima ART**
- **Il cambio di terapia a viremia controllata**
- **Il paziente HTE, MDR, LTO**

# Evoluzione della Terapia Antiretrovirale



# Life Expectancy After HIV Diagnosis 2008–2018, US

Azfar-E-Alam Siddiqi, et al. Abstract 761

- During 2008–2018, overall, the life expectancy for people with diagnosed HIV increased by 4.22 years or 15%
- Yet, the life expectancy for people with diagnosed HIV remains lower than that for the general U.S. population

## RESULTS

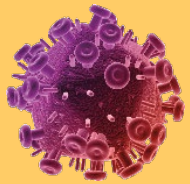
- In 2018, among persons with late-stage disease (HIV Stage 3 [AIDS]) at diagnosis, the LE was considerably lower (27.16 years, CI 27.02–27.31) compared to persons with disease not at stage 3 (34.39 years (CI 34.34–34.43).

# Selecting an Optimal ARV Regimen

*"The goal of antiretroviral therapy is to provide a potent, safe, tolerable, and easy-to-adhere-to regimen in order to achieve sustained virologic control"*
- DHHS Guidelines 2019

## Select Features of an Optimal ARV Regimen[1]

- High Viral Suppression Rates



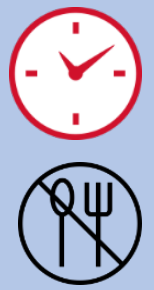
- Low Pill Burden

- Less Toxicity

- Better Tolerability

- Low Drug Interactions Potential

- Convenience



- High Barrier to Resistance

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf Accessed October 2020

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# Recommended First-line ART Regimens 2020/21

| ARV | EACS[1] | US DHHS[2] | IAS-USA[3] | WHO[4] |
|---|---|---|---|---|
| DTG | DTG + TAF/FTC or TDF/FTC or TDF/3TC | DTG + (TAF or TDF) + (FTC or 3TC) | DTG + TAF/FTC or TDF/FTC or TDF/3TC | DTG + TDF + 3TC (or FTC) |
| DTG | DTG + ABC/3TC† DTG/ABC/3TC† | DTG/ABC/3TC† | -- | -- |
| BIC | BIC/TAF/FTC | BIC/TAF/FTC | BIC/TAF/FTC | |
| RAL | RAL + TAF/FTC or TDF/FTC or TDF/3TC | -- | -- | -- |
| DTG | DTG/3TC* | DTG/3TC* | DTG/3TC* | |
| DOR | DOR + TAF/FTC or TDF/FTC or TDF/3TC DOR/TDF/3TC | -- | -- | -- |

*DTG/3TC: Avoid in patients with HBV and HIV-1 RNA >500,000 c/mL; in some guidelines, avoid in those starting ART before results of GT resistance testing are available or with CD4+ cell count <200/µL. †If patient is HLA-B*5701 negative.


1. eacsociety.org/media/final2021eacsguidelinesv11.0_oct2021.pdf
2. clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf
3. jamanetwork.com/journals/jama/fullarticle/2771873 4. who.int/publications/i/item/9789240031593

# Our choice HAS been driven to avoid Toxicity Profile of Certain ARVs

| Class | Agent | Select AEs |
|---|---|---|
| NRTI | ABC | Ischemic heart disease |
| | TDF | [illegible] |
| NNRTI | EFV | Depression, sleep disturbance, headache, suicidal ideation |
| PI | ATV | [illegible] |
| | DRV | Ischemic heart disease, nephrolithiasis |
| | LPV | [illegible] |

So we have moved towards using INSTIs and TAF

EACS Guidelines. October 2018.

POZNIAK, ICAR 2020

# Terapia ART nel naive 2022

Non può essere TDF or ABC based

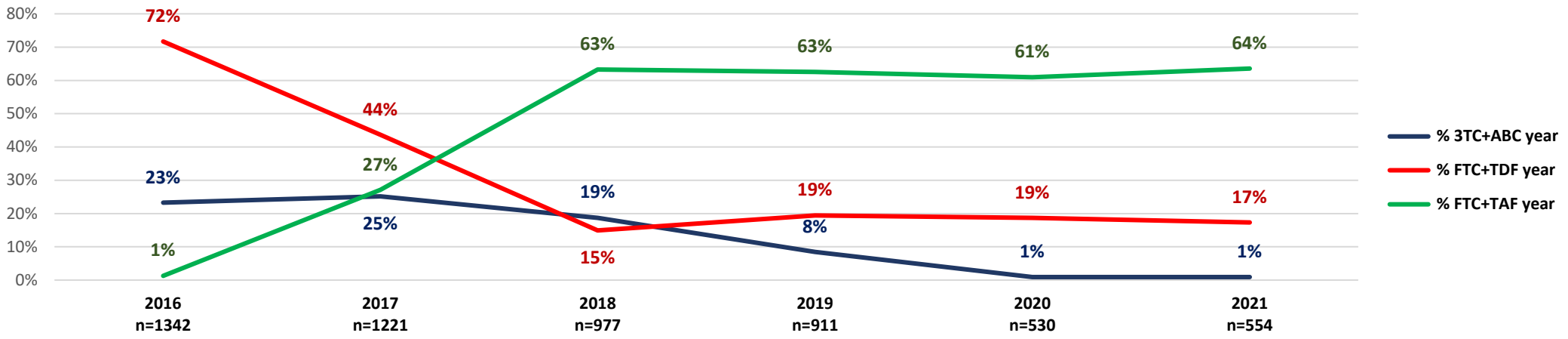
Può essere 2DR

Deve essere INI based

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Italian Cohort I. C. O. N. A. Naive Antiretrovirals

## Proportion of patients treated with TDF/FTC or TAF/FTC or ABC/3TC as firstline backbone, according to last 6 calendar years



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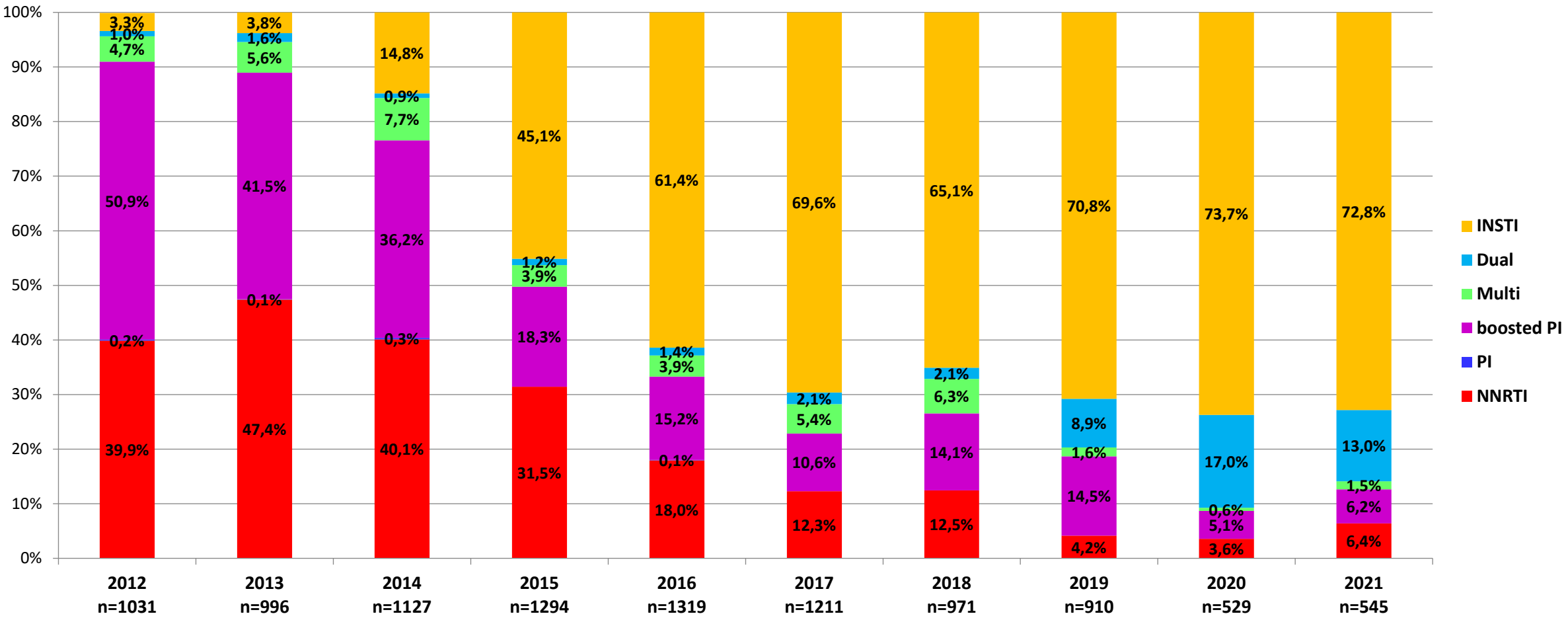
ITALIAN COHORT NAIVE ANTIRETROVIRALS

# Proportion of usage of different ART classes as third drug in first line regimen according to calendar year of starting



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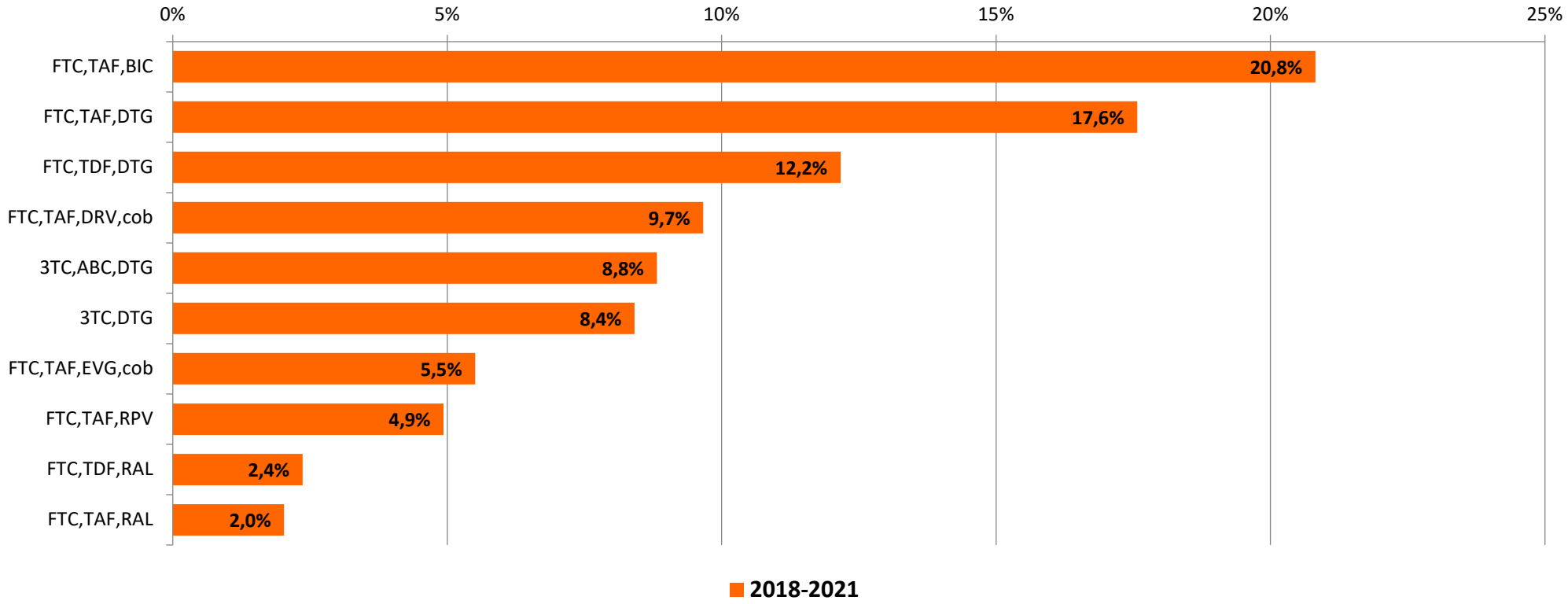
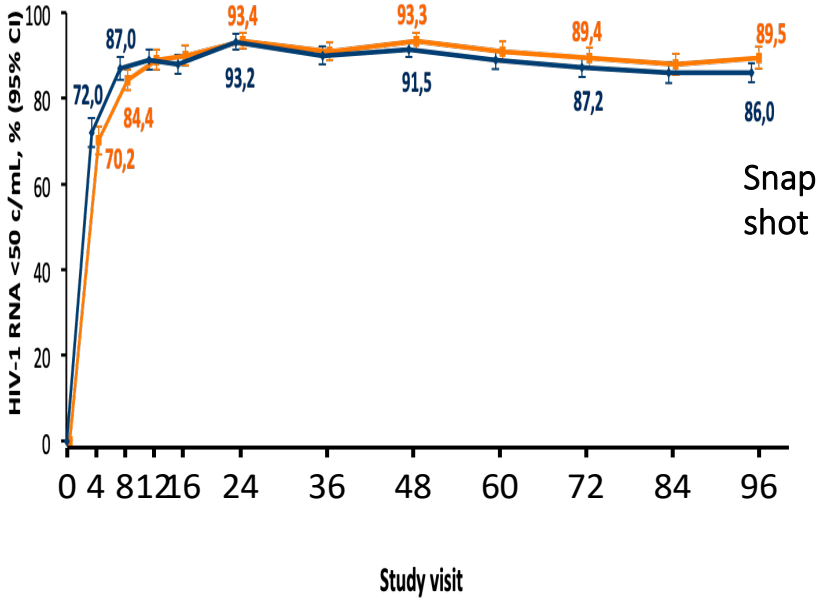
# Most frequent regimens used in first line according to calendar period of starting



## GEMINI-1 AND GEMINI-2, PHASE III STUDY

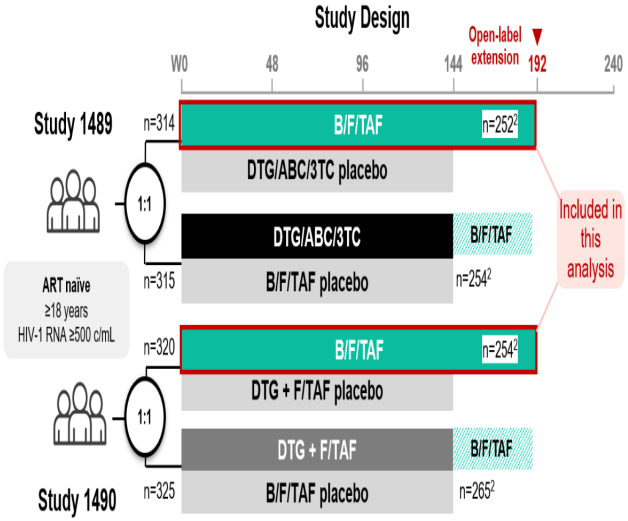


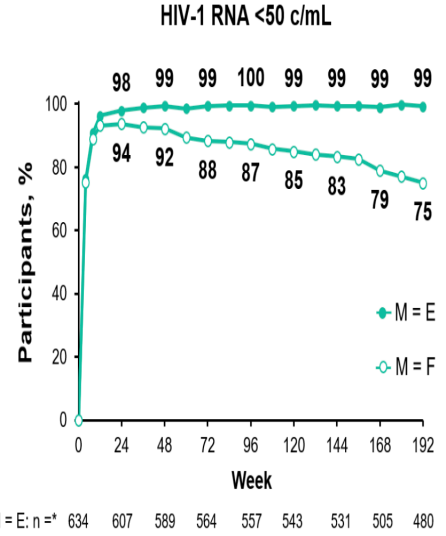

Snap shot

*Cahn P, IAS 2019, Abs. WEAB0404LB*

Pooled Analysis 1489/1490: B/F/TAF in **ART-Naïve**, W192

## 4-year Follow-up of B/F/TAF in Treatment-Naïve PLWH




*Participants with non-missing HIV-1 RNA value
M=E, missing=excluded; M=F, missing=failure

**High rates of virologic suppression were achieved and maintained through 192W of follow-up**

Arribas J, et al. vIAS 2021. PEB151

# BHIVA Interim Guidance Recommends B/F/TAF as 1st line ART Choice in Treatment Naïve Setting During COVID-19 Epidemic

## Considerations

Limiting factors considered in the context of COVID-19 with first line ART choice:

- limited access to baseline resistance testing;
- minimized patient visits for viral load and safety monitoring tests;
- limited access to HIV pharmacist input for DDI counselling; and adherence support

Key requirements of initial ART during the COVID pandemic:

- *Well-tolerated regimen*
- *High efficacy*
- *High barrier to resistance*
- *Low risk of toxicity*
- *Ideally STR*
- *No food requirements*

## First-line ART Recommendations

*This interim guidance is intended for temporary use during the COVID-19 pandemic in the UK where service capacity is sub-optimal, has not been subject to the usual rigorous guideline development process. We advise that where any service has the capacity to operate as they would usually, they continue to do so, but where circumstances limit access to investigations or appointments, the appropriate parts of this guidance are followed accordingly.*

| | |
|---|---|
| **Recommended** | ***B/F/TAF*** *unless contra-indicated due to: DDIs or new diagnosis in a pregnant woman* |
| **Alternative** | Whichever alternative regimen is clinically appropriate and acceptable to the patient can be used if B/F/TAF is unsuitable or not tolerated, based on individual patient characteristics and the capacity of a service to provide advice and monitoring |

## Impact

The guidance highlights the rationale for not using PI-based ART (increased risk of short and long-term toxicity and tolerability issues), and TDF-based regimes (renal monitoring requirement at initiation).

ART, anti retroviral therapy; DDI, drug-drug interaction; STR, single tablet regimen

BHIVA interim ART guidelines COVID-19 v2 07082020. Accessed 18 SEP 2020

# NAIVE

- **Triplice**
  - **BIC/TAF/FTC (triplice STR)**
  - **DTG+TAF/FTC  (+ costosa)**
  - **DTG/3TC/ABC (HLA B57, rischio CV)**
  - **DOR +TAF/FTC (2 compresse) DOR/TDF/FTC (ruolo del TDF su osso e rene)**
- **Duplice**
  - **DTG/3TC (duplice STR, meno costosa, attendere GRT? HBV?)**

# 2022 update quali argomenti ?

- La prima ART
- **Il cambio di terapia a viremia controllata**
- Il paziente HTE, MDR, LTO

# Terapia ART nello switch 2022

Non può essere TDF/ABC based

Può essere NNRTI based

Può essere INI based

# Attenzione

- **Effetti collaterali**
  - **Rene (TDF), osso (TDF), peso (TAF? DTG?), diabete PI, rischio CV (PI, ABC)**
- **Riattivazione di HBV**
  - **TDF o TAF Sparing**

ICAR 2022 Bergamo 14-16 Giugno 2022 14° CONGRESSO NAZIONALE

2022 14° CONGRESSO NAZIONALE

# Reactivation of hepatitis B virus is a frequent event in anti-HBc positive/HBsAg-negative HIV-infected patients switching to Tenofovir sparing therapy as revealed by highly sensitive HBV assays

**Romina Salpini**, Stefano D'Anna, Mohammad Alkhatib, Lorenzo Piermatteo, Alessandro Tavelli, Eugenia Quiros, Antonella Cingolani, Chiara Papalini, Stefania Carrara, Vincenzo Malagnino, Massimo Puoti, Loredana Sarmati, Antonella d'Arminio Monforte, Francesca Ceccherini Silberstein, Valentina Svicher for the Icona Foundation Study Group

TOR VERGATA UNIVERSITÀ DEGLI STUDI DI ROMA

Presenting author. Romina Salpini, University of Rome Tor Vergata

Fondazione Icona

**BcAb+/HBsAg– patients with HIV-**
**aring therapy.**

**intrahepatic HBV reservoir and is**
**nmunocompromission.**

**on liver damage and HIV infection**
**deserves further investigation.**

**These findings highlight the importance of a proper screening and continuous monitoring of anti-HBc+/HBsAg- patients with HIV infection, particularly if candidated to therapeutic switch not including TDF/TAF**

**Ultrasensitive assays for serum HBV-DNA, together with novel HBV biomarkers (HBV-RNA, q-antiHBc), can optimize the management of HBcAb+/HBsAg– patients with HIV infection.**

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ICAR 2022
Bergamo
14-16 Giugno
2022
14° CONGRESSO NAZIONALE

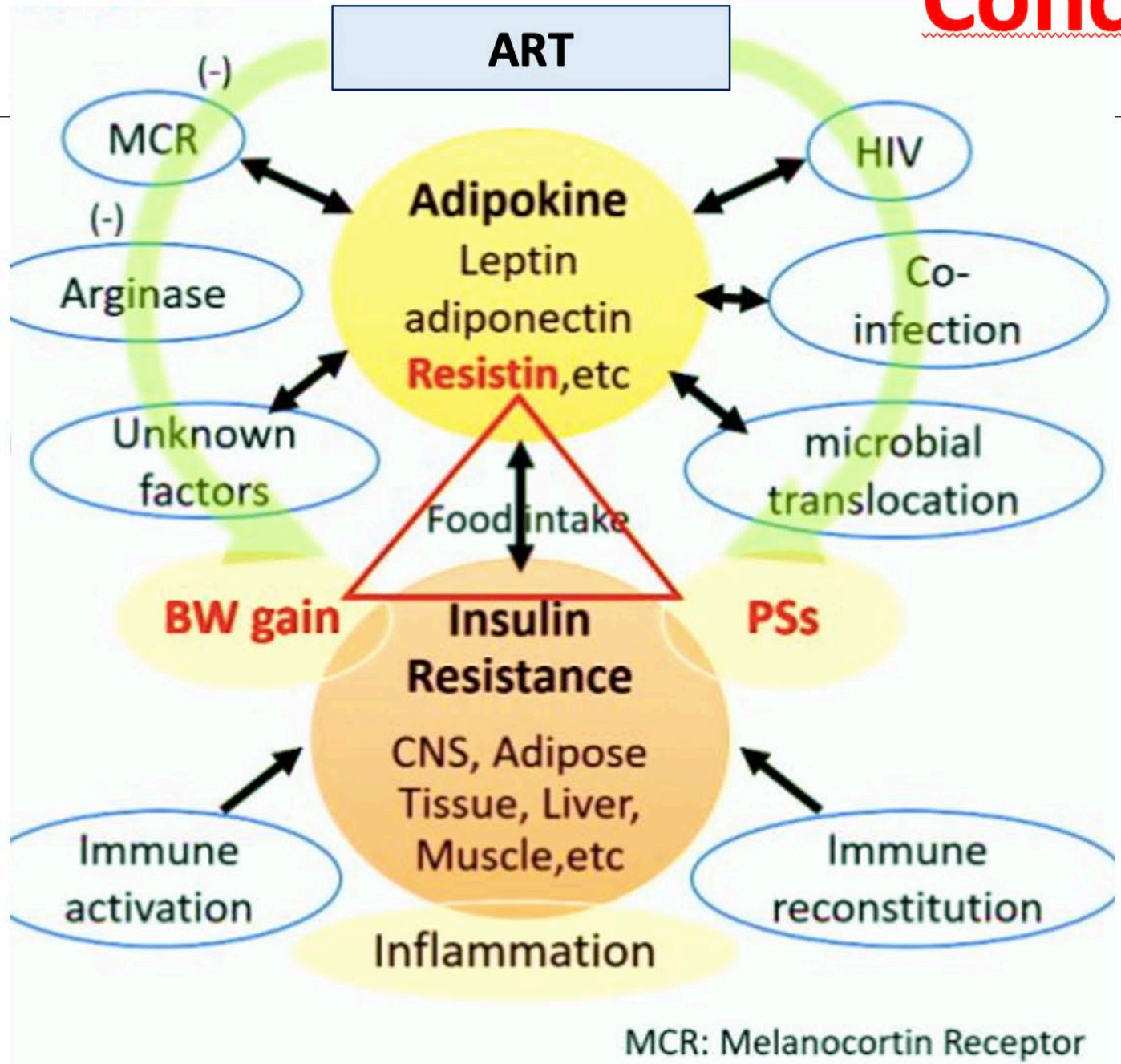
# Pathogenetic aspects of weight gain under ART

**Lucia Taramasso**

*Clinica Malattie Infettive IRCCS Policlinico San Martino di Genova*

Bergamo, 16 Giugno 2022

# Conclusions




*CYP2B6*

Energy expenditure

Lifestyle

R. Minami et al., CROI 2020, OP, Abstract 670

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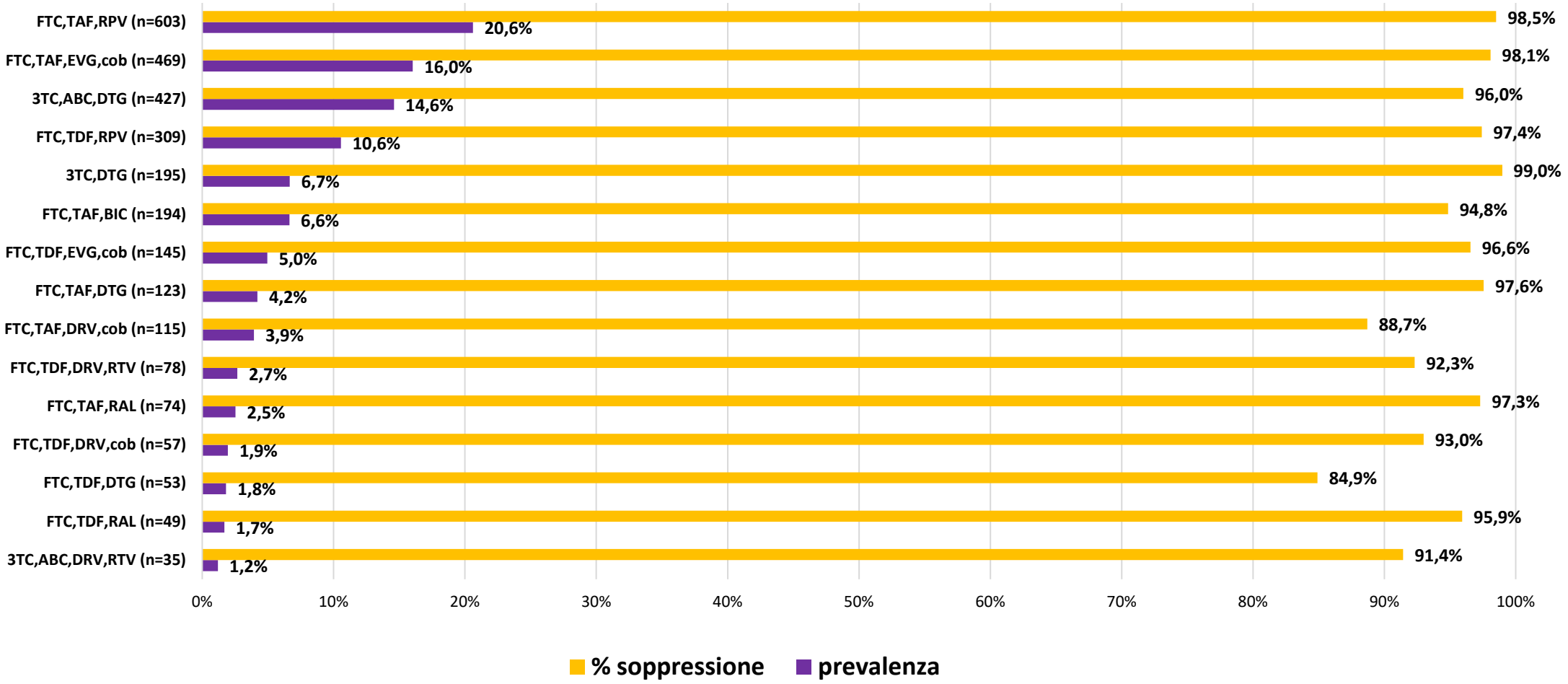
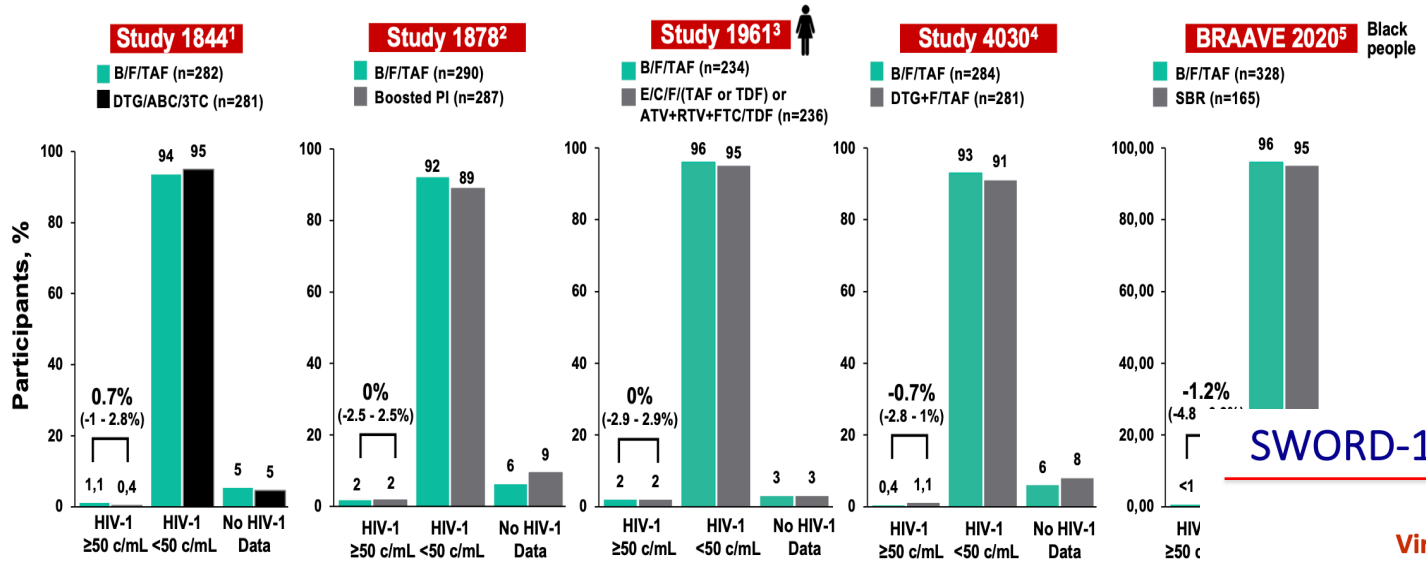
ITALIAN COHORT NAIVE ANTIRETROVIRALS

# Prevalence of VL suppressed patients starting a second line regimen from 2014 within 1 year of follow-up (n=2926, therapy prevalence >1%)



# Virologic Outcome by FDA Snapshot Analysis through W48*




**Switching to BFTAF has non-inferior efficacy in all suppressed adults switched fi multiple regimens through W48 and in a study of Black adults through W24**

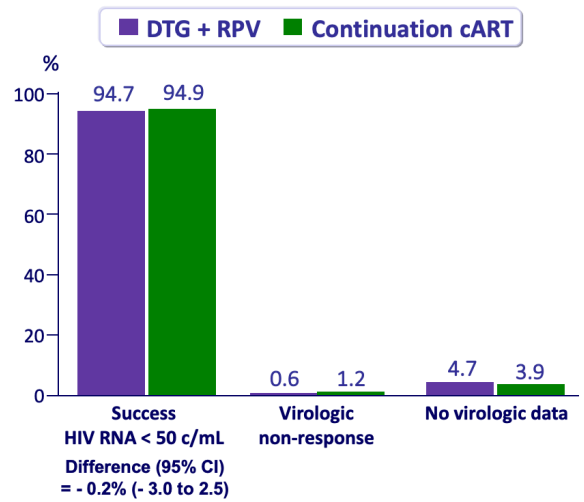
SBR, stay on baseline regimen

*BRAAVE 2020 results through W24

1. Molina JM, et al. *Lancet HIV* 2018;5:e357–65
2. Daar E, et al. *Lancet HIV* 2018;5:e347–56.
3. Kityo C, et al. *JAIDS* 2019. 82(3):321-328
4. Sax P, et al. CID 2021;73(2):e485–93;
5. Hagins D, et al. CROI 2020. Boston, MA. Oral 36

## SWORD-1 & 2 Studies: Switch to DTG + RPV

**Virologic outcome at W48 (ITT-E, snapshot)**



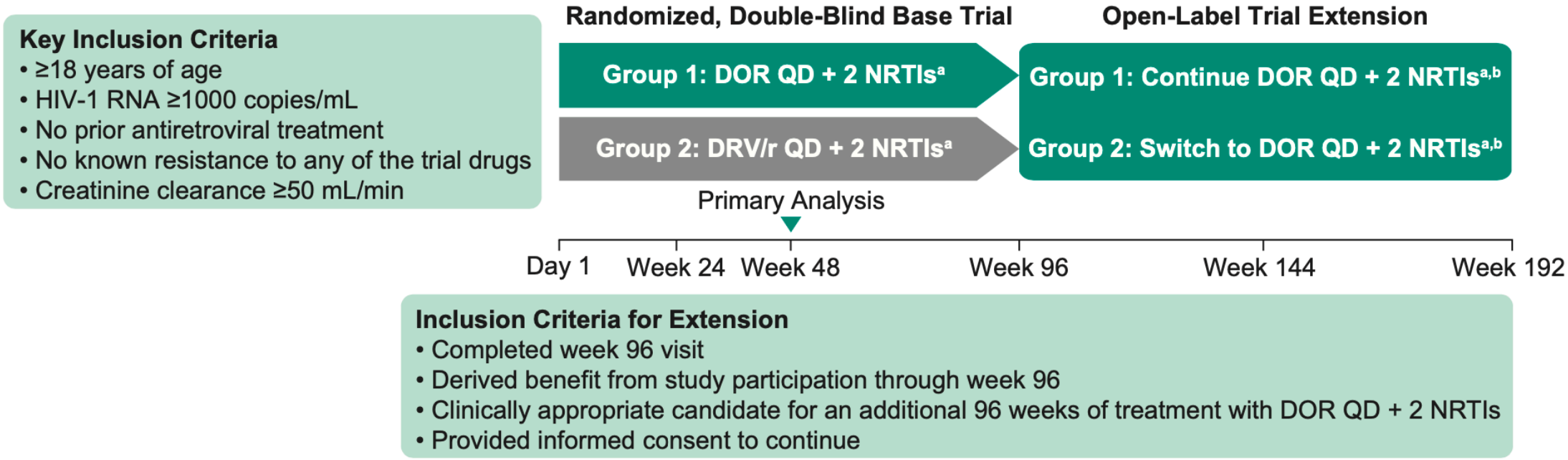

**Other virologic results at W48**

- HIV RNA < 50 c/mL (ITT-E snapshot)
  - SWORD-1
    - 95% DTG + RPV
    - 96% continuation cART
    - Adjusted ≠: - 0.6% (95% CI: - 4.3 to + 3.0)
  - SWORD-2
    - 94% DTG + RPV
    - 94% continuation cART
    - Adjusted ≠: 0.2% (95% CI: - 3.9 to + 4.2)
- Confirmed virologic failure: HIV RNA ≥ 50 c/mL, retest ≥ 200 c/mL
  - DTG + RPV, N = 2
    - Emergence of NNRTI resistance mutation (K101K/E)
  - Continued cART, N = 2
    - No mutations

*Llibre JM. Lancet. 2018;391:839*

# The Efficacy and Safety of Maintenance With Doravirine Plus Two NRTIs After Initial Suppression in Adults With HIV-1 in the DRIVE-FORWARD

## Figure 1. DRIVE-FORWARD Study Design




ABC/3TC, abacavir and lamivudine; DOR, doravirine; DRV/r, ritonavir-boosted darunavir; NRTI, nucleos(t)ide reverse transcriptase inhibitor; QD, once daily; TAF, tenofovir alafenamide; TDF/FTC, tenofovir disoproxil fumarate and emtricitabine.

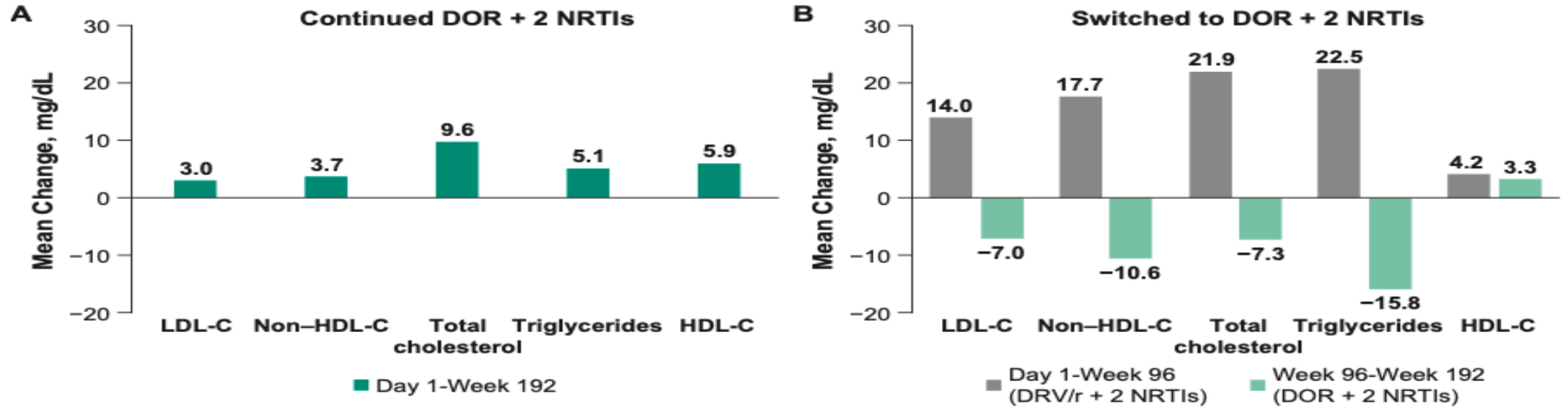
[a]Investigator-selected NRTI was either TDF/FTC or ABC/3TC.

[b]Changes in NRTIs between the base trial and open-label extension were made on a case-by-case basis; as needed by agreement of the investigator and the sponsor, TAF was permitted.

Presented at IDWeek 2021; September 29–October 3, 2021; Virtual

# The Efficacy and Safety of Maintenance With Doravirine Plus Two NRTIs After Initial Suppression in Adults With HIV-1 in the DRIVE-FORWARD Clinical Trial: Results From the Study Extension Through 192 Weeks

**Figure 5. Change in Fasting Lipids**

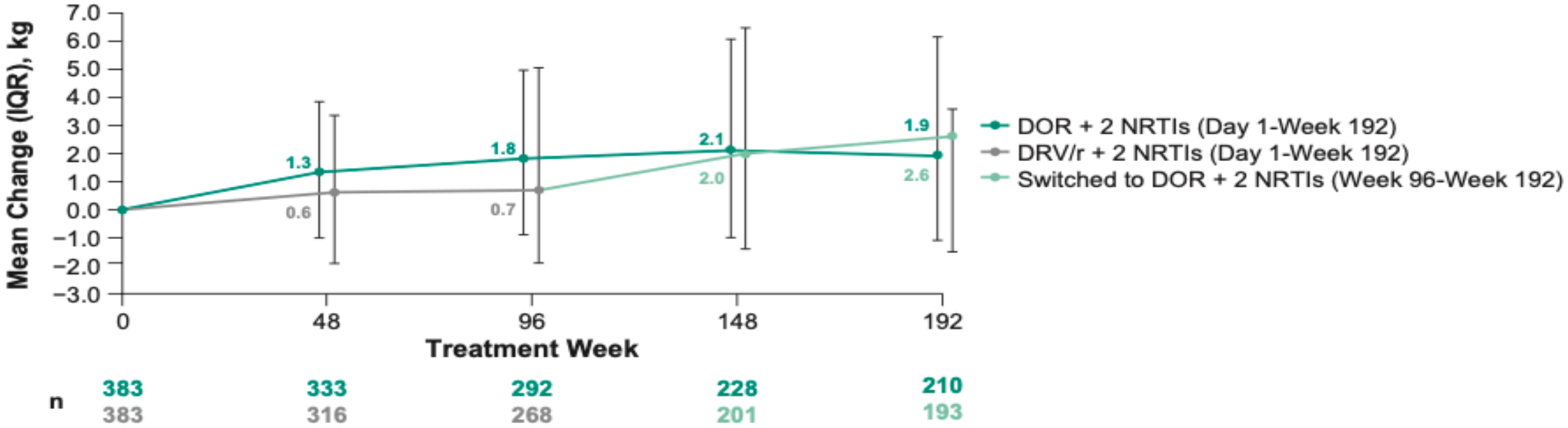



HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

- Participants who continued DOR + 2 NRTIs maintained a favorable lipid profile, with minimal changes in all lipid measures
- Participants who switched from DRV/r + 2 NRTIs had substantial reductions in low-density lipoprotein cholesterol, non–high-density lipoprotein cholesterol, total cholesterol, and triglycerides
- There were only minimal changes in the total cholesterol:high-density lipoprotein cholesterol ratio for participants who continued DOR + 2 NRTIs and those who switched to DOR + 2 NRTIs (−0.2 and −0.4, respectively)

# The Efficacy and Safety of Maintenance With Doravirine Plus Two NRTIs After Initial Suppression in Adults With HIV-1 in the DRIVE-FORWARD Clinical Trial: Results From the Study Extension Through 192 Weeks

## Figure 6. Change in Weight, Day 1 through Week 192




IQR, interquartile range.

- Participants who continued DOR + 2 NRTIs had minimal weight gain after week 96 (median 1.0 kg) and a small increase in weight from baseline through week 192 (1.9 kg)
- Participants who switched to DOR + 2 NRTIs had a small weight increase after week 96 (median 1.5 kg), similar to the median weight gain observed in the base trial: DOR + 2 NRTIs, 1.8 kg; DRV/r + 2 NRTIs, 0.7 kg

Presented at IDWeek 2021; September 29–October 3, 2021; Virtual

AIDS Research and Human Retroviruses, Ahead of Print |

# Long-Term Effectiveness of Rilpivirine-Based Single-Tablet Regimens in a Seven-Year, Two-Center Observational Cohort of People Living with HIV

Lucia Taramasso, Sergio Lo Caputo, Laura Magnasco, Federica Briano, Mariacristina Poliseno, Serena Rita Bruno, Sergio Ferrara, Rachele Pincino, Giovanni Sarteschi, Sabrina Beltramini, Elisabetta Sasso, Sara Mora, Mauro Giacomini, Matteo Bassetti, and Antonio Di Biagio

**Published Online:** 15 Mar 2022 | https://doi.org/10.1089/aid.2021.0161

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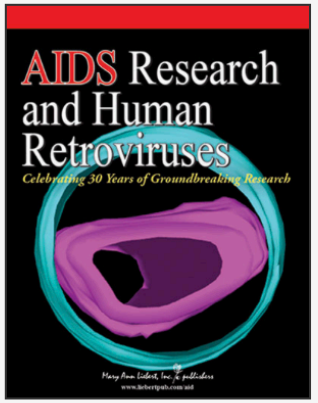


## Information



**To cite this article:**

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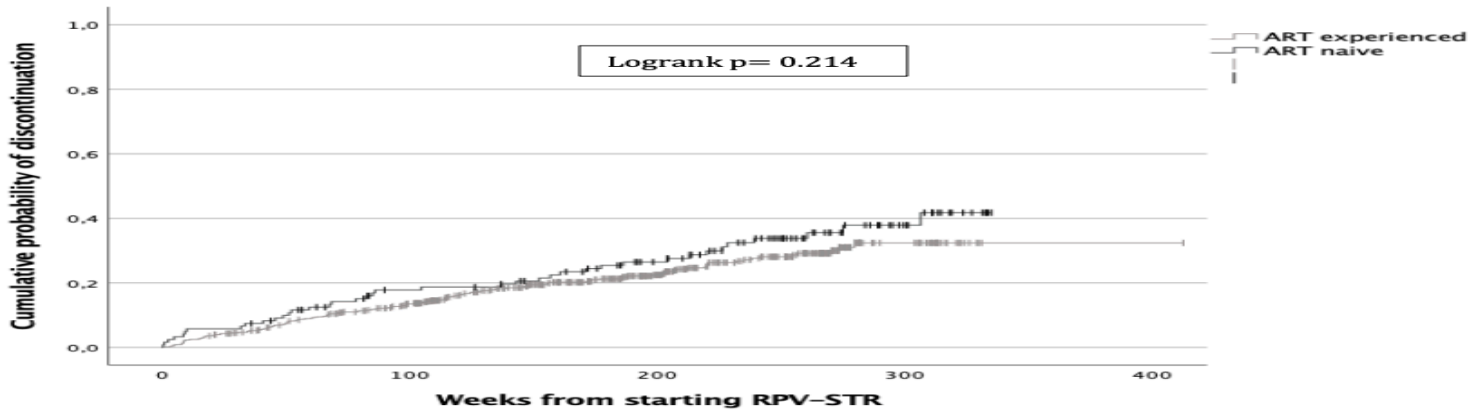
**Table 1.** Characteristics of study participants, according to being ART-naïve or -experienced.

| Characteristic | ART-naïve patients (n=123) | ART-experienced patients (n=561) | p-value |
|---|---|---|---|
| Male sex, number (%) | 92 (74.8) | 372 (66.3) | 0.068 |
| Age in years, mean ± SD | 46.1 ± 11.5 | 54.1 ± 10.7 | **<0.001** |
| Ethnicity, n (%) | | | **0.006** |
| Caucasian | 99 (80.5) | 509 (90.7) | |
| African | 11 (8.9) | 17 (3.0) | |
| Hispanic | 12 (9.8) | 33 (5.9) | |
| Other | 1 (0.8) | 2 (0.4) | |
| Risk factor for HIV infection, n (%) | | | **0.002** |
| MSM | 28 (22.8) | 80 (14.3) | |
| Heterosexual contact | 24 (19.5) | 170 (30.3) | |
| Intravenous drug use | 18 (14.6) | 117 (20.9) | |
| Mother-to-child transmission | 0 (0.0) | 15 (2.7) | |

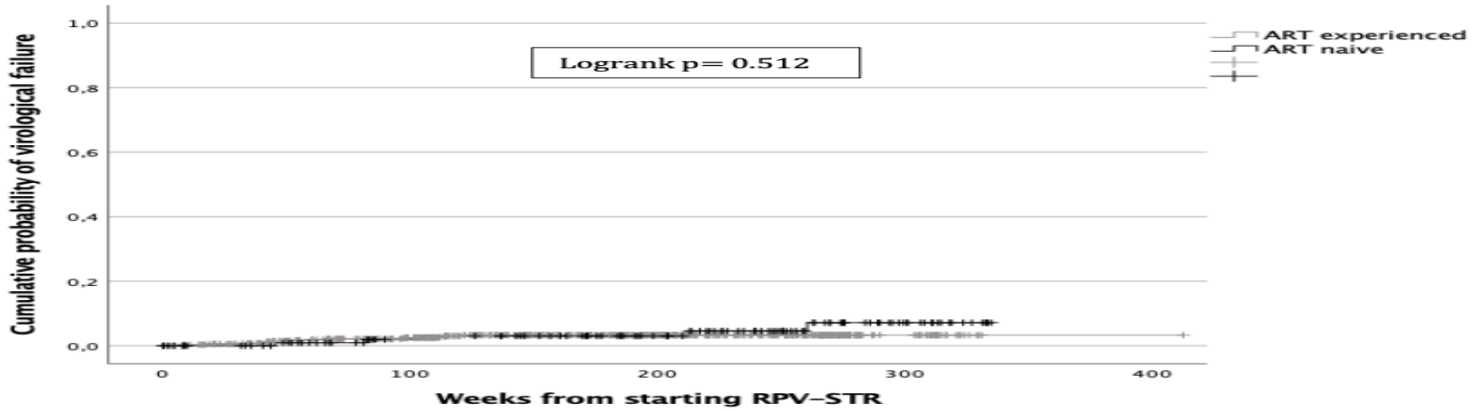
| | | | |
|---|---|---|---|
| HBsAg positive, n (%) | 4 (3.3) | 12 (2.1) | 0.057 |
| HCV-Ab positive, n (%) | 25 (20.3) | 186 (33.2) | **0.001** |
| Zenith HIV RNA ($log_{10}$ copies/mL), mean ± SD | 4.89 ± 5.37 | 5.55 ± 6.26 | **<0.001** |
| Nadir of $CD4^+$ (cells/mL), mean ± SD | 415 ± 212 | 257 ± 196 | **<0.001** |
| Available GRT at baseline, n (%) | 58 (47.2) | 144 (25.7) | **<0.001** |
| Years between HIV diagnosis and initiation of RPV, median (IQR) | 1.7 (0.2-7.2) | 14.8 (8.2-22.9) | **<0.001** |
| Number of previous ART regimens, mean ± SD | N/A | 3.6 ± 2.7 | - |
| Previous STR regimen before RPV-STR, n (%) | N/A | 278 (49.6) | - |
| Duration of RPV-STR treatment in weeks, mean ± SD | 192.5 ± 99.5 | 173.3 ± 85.6 | **0.030** |
| Discontinuation of RPV-STR, n (%) | 41 (33.3) | 132 (23.5) | 0.119 |

| | | | |
|---|---|---|---|
| Reasons for discontinuation of RPV-STR, n (%) | | | 0.119 |
| Unknown | 2 (1.6) | 3 (0.5) | |
| Virological failure | 5 (4.1) | 17 (3.0) | |
| Simplification | | | |
| Optimization | | | |
| Adverse event | | | |
| Drug-drug intera | | | |
| Lost to follow-up | | | |
| Deceased/moved | | | |
| Poor compliance | | | |

(a)




(b)



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VOCABRIA

cabotegravir sospensione per iniezione

**18 maggio 2022**

REKAMBYS

rilpivirina sospensione per iniezione

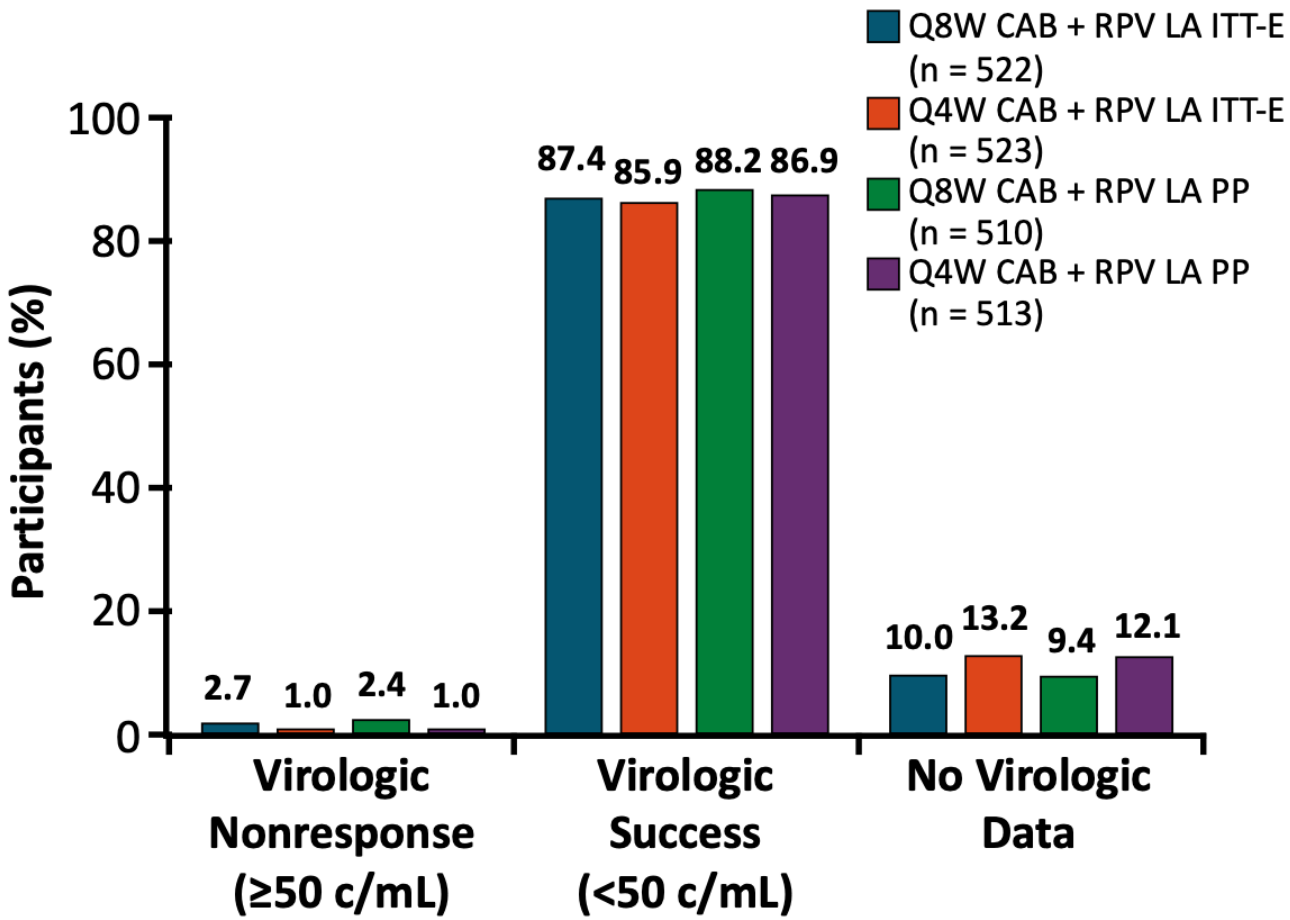
**Riassunto delle caratteristiche del prodotto**

**18 maggio 2022**

# Indicazioni

- **Cabotegravir & Rilipvirina LA: Trattamento negli adulti in soppressione virologica, in regime stabile, senza evidenza presente o passata di resistenza virale e di precedente fallimento virologico a NNRTI e/o INSTI**

# ATLAS-2M: Wk 152 Virologic Outcomes




- 2 additional participants (both male at birth, BMI <30 kg/m$^2$) in Q8W arm met CVF criteria between Wk 96 and 152 (Wk 112, 120)
  - At BL, neither had RAMs; participant with A6 subtype had L74I integrase polymorphism

| Country | Baseline | At Failure | | |
|---|---|---|---|---|
| | HIV-1 Subtype | HIV-1 RNA (c/mL) | RPV RAMs | INI RAMs |
| Germany | B | 24,221 | E138A+ M230M/L | Q148R |
| Russia | A6* | 59,467 | E138A+ Y181Y/C | Q148R |

*Originally classified as A1; later reclassified as A6 upon reanalysis

- Through Wk 152, 13 participants had CVF: Q8W, n = 11 (2%); Q4W, n = 2 (<1%)
  - None with injection >7 days late

Overton. CROI 2022. Abstr 479.

# ATLAS-2M: ISRs and Treatment Satisfaction Through Wk 152

| Injection-Site Reactions | Q8W (n = 522) | Q4W (n = 523) |
|---|---|---|
| Participants who received ≥1 injection, n (%) | 516 (99) | 517 (99) |
| Number of injections | 20,563 | 39,478 |
| ISR events, n | 4168 | 5494 |
| ▪ Injection site pain, n (% of injections) | 3189 (16) | 4180 (11) |
| ▪ Injection site nodule, n (% of injections) | 259 (1) | 457 (1) |
| Grade 3, n (% of ISR events) | 54 (1) | 50 (1) |
| Median duration, days (IQR) | 3 (2-5) | 3 (2-5) |
| Participants withdrawing for injection-related reasons, n (% ) | 8 (2) | 13 (3) |

- HIV treatment satisfaction questionnaire scores from participants without prior CAB
  - Total mean scores significantly improved from BL to Wk 152 for both groups
  - Adjusted mean change from BL significantly favored Q8W dosing at Wk 24, 48, and 152

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# Switch HIV-RNA <50 copies/mL

- **Triplice**
  - **BIC/TAF/FTC (triplice INSTI, STR)**
  - **RPV/TAF/FTC (triplice NNRTI, STR)**
  - **DOR/TDF/FTC (triplice NNRTI, STR, Attenzione TDF!)**

- **Duplice Orale**
  - **DTG/3TC (duplice STR, meno costosa)**
  - **DTG/RPV**

**Duplice IM**

**LA: Cabotegravir/Rilpivirina**

NEW
2022

# 2022 update quali argomenti ?

- La prima ART
- Il cambio di terapia a viremia controllata
- **Il paziente HTE, MDR, LTO**

# Already available from now

Rukobia (fostemsavir) extended-release tablets · 600 mg

30 luglio 2020

7 ottobre 2021

NEW Trogarzo™ (ibalizumab-uiyk) Injection

No EU

## Indicazioni

- **Fostemsavir: Trattamento, in associazione ad altri antiretrovirali, di pazienti con infezione da HIV e virus MDR, in fallimento virologico**
- **Ibalizumab: Trattamento, in associazione ad altri antiretrovirali, di pazienti con infezione da HIV e virus MDR, in fallimento virologico**

# From Phase II trials

## ORAL

- **Islatravir** (NRTTI)
- **Lenacapavir** (Capsid Inhibitor)
- **MI 254** (Maturation Inhibitor)

## INJECTABLE

- **Albuvirtide** (Entry Inhibitor)
- **bNAabs** (Attachment-Fusion)
- **Lenacapavir** (Capsid Inhibitor)
- **Elsulfavirine** (NNRTI)
- **Islatravir** (NRTTI)
- **MI 934** (Maturation Inhibitor)

# Conclusioni

La ART non può essere per tutti uguale

Deve seguire i trials clinici

Il 2022 sarà l'anno degli iniettivi che cambieranno lo scenario

Oggi però abbiamo terapie efficaci e ben tollerate anche per os