# Update dagli studi clinici alla pratica clinica nella popolazione femminile


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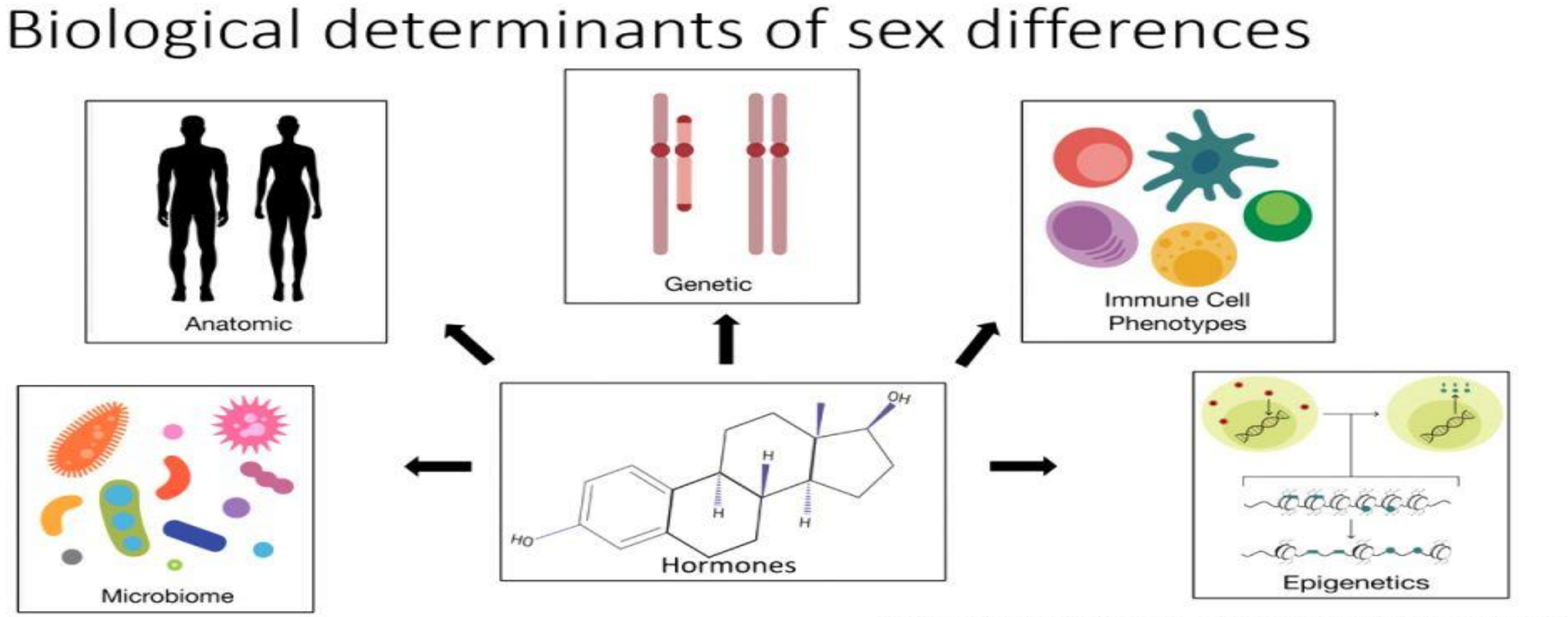
# Agenda

- Sex differences
- Observational studies
- Update on HIV clinical trials in women

# Women / sex differences:

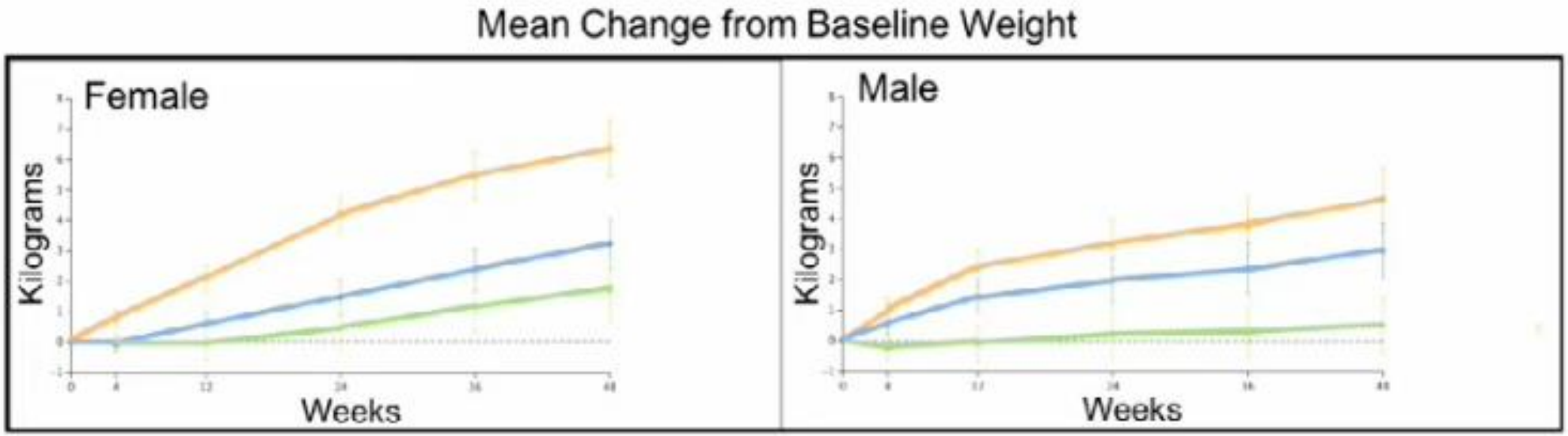
## Scully CROI 2020 (abst 63)




Scully, E *Curr HIV/AIDS Reports*, 2018, *Pathogens and Immunity 2019*

# Unanticipated lessons: Drug-drug interactions and adverse effects

- Efavirenz reduces contraceptive efficacy of levonorgestrel
- Sex specific weight gain from specific ART regimens

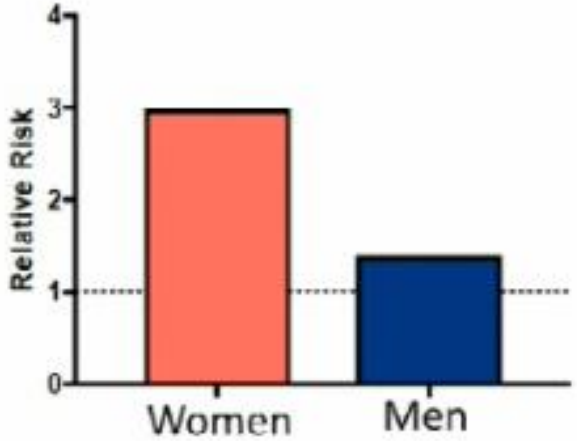



**Scully CROI 2020 (abst 63)**

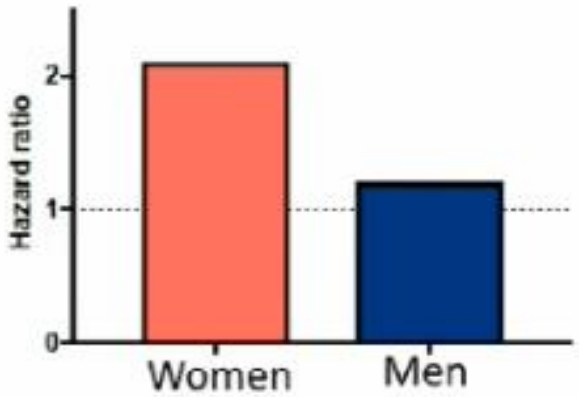
*Scarsi KK et al, CID, 2016; Venter et al., NEJM 2019*

# HIV drives a greater increase in risk of vascular disease in women

- Myocardial infarction




- Cerebrovascular disease

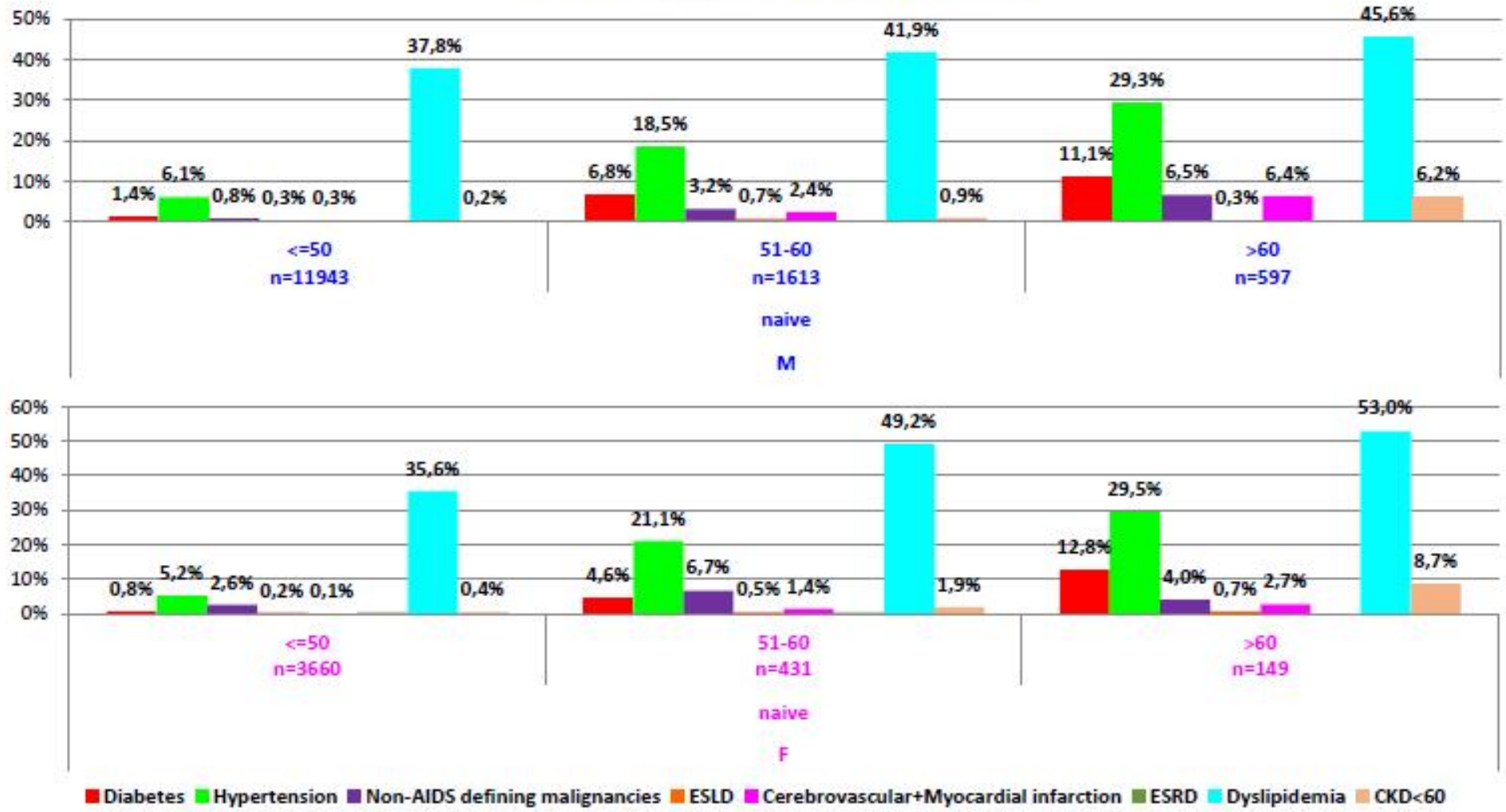



*Triant et al., J Clin Endocrinol Metab, 2007; Raghavan et al, Curr HIV/AIDS Reports, 2018; Chow et al., AIDS, 2018; Lake et al.,Abstract 645; Haberlen et al, Abstract 642;*

**Scully CROI 2020 (abst 63)**

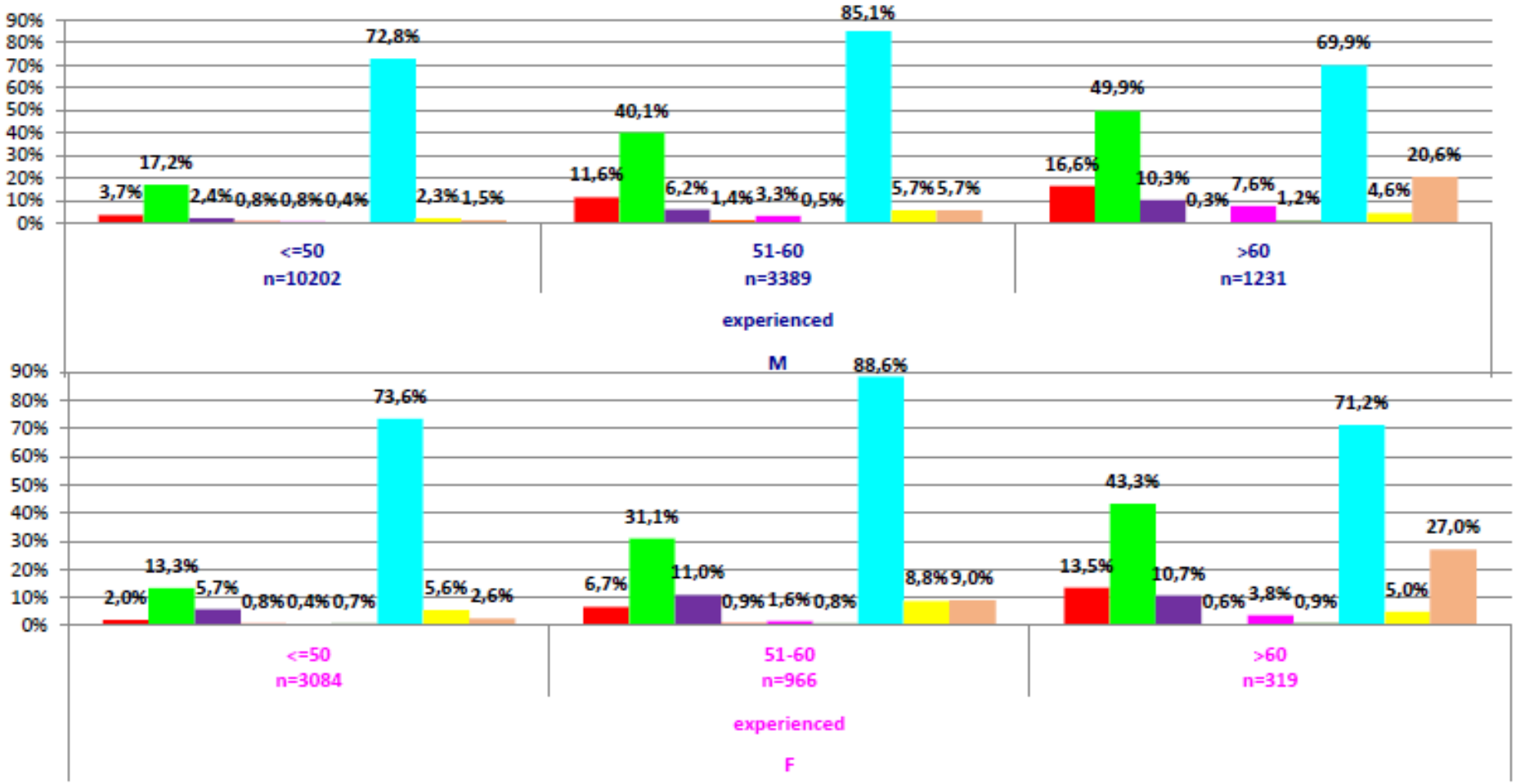
Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

# Prevalence of different non-communicable comorbidities at different age strata at enrolment, according to gender

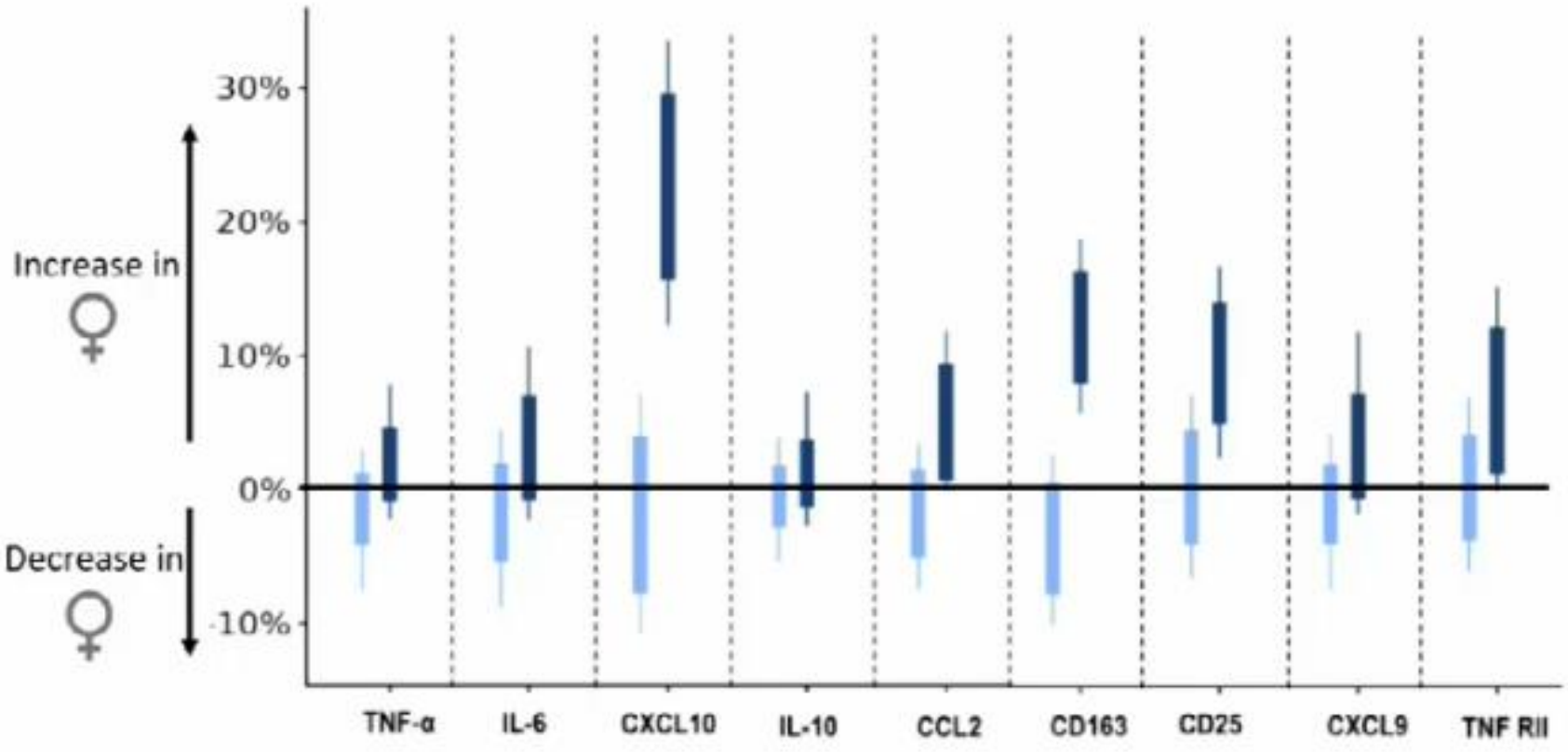


Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

# Prevalence of different non-communicable comorbidities at different age strata in ART - treated patients, according to gender



# Patterns of residual inflammation differ between men and women

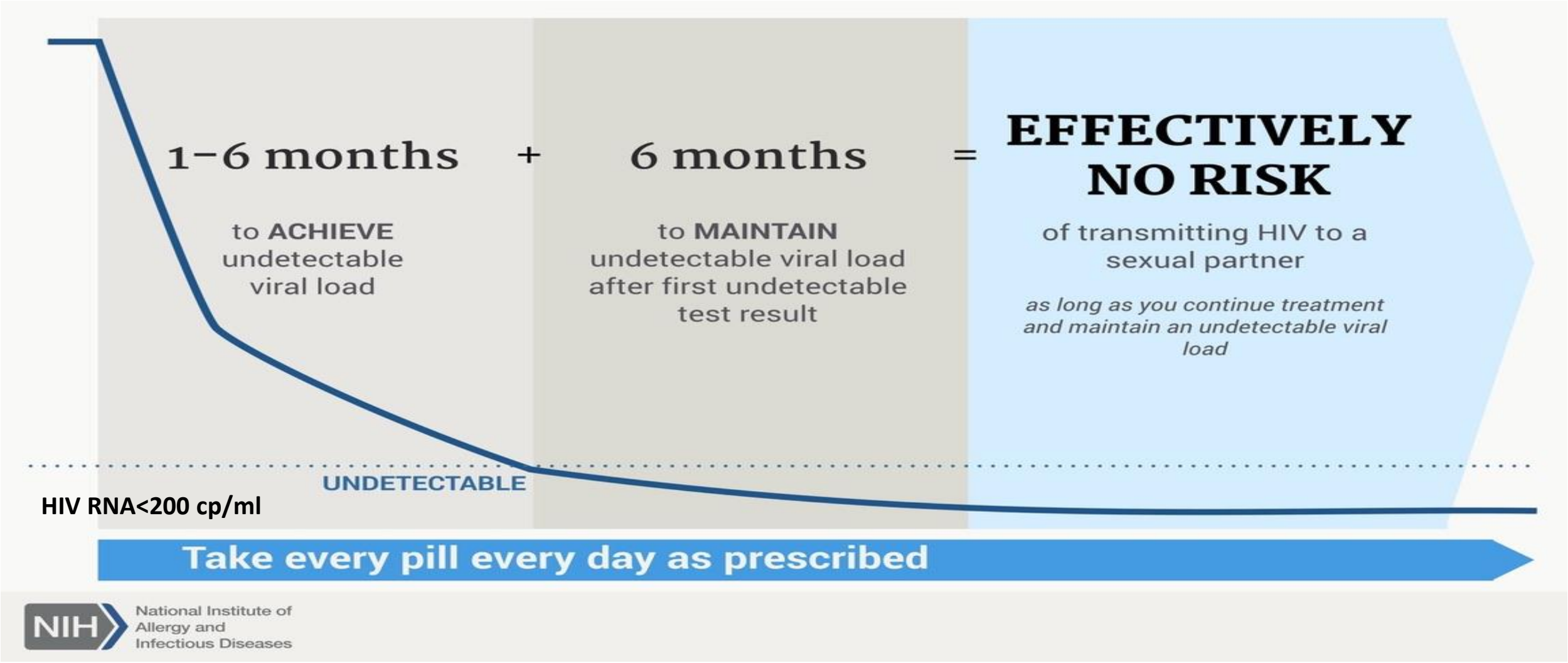




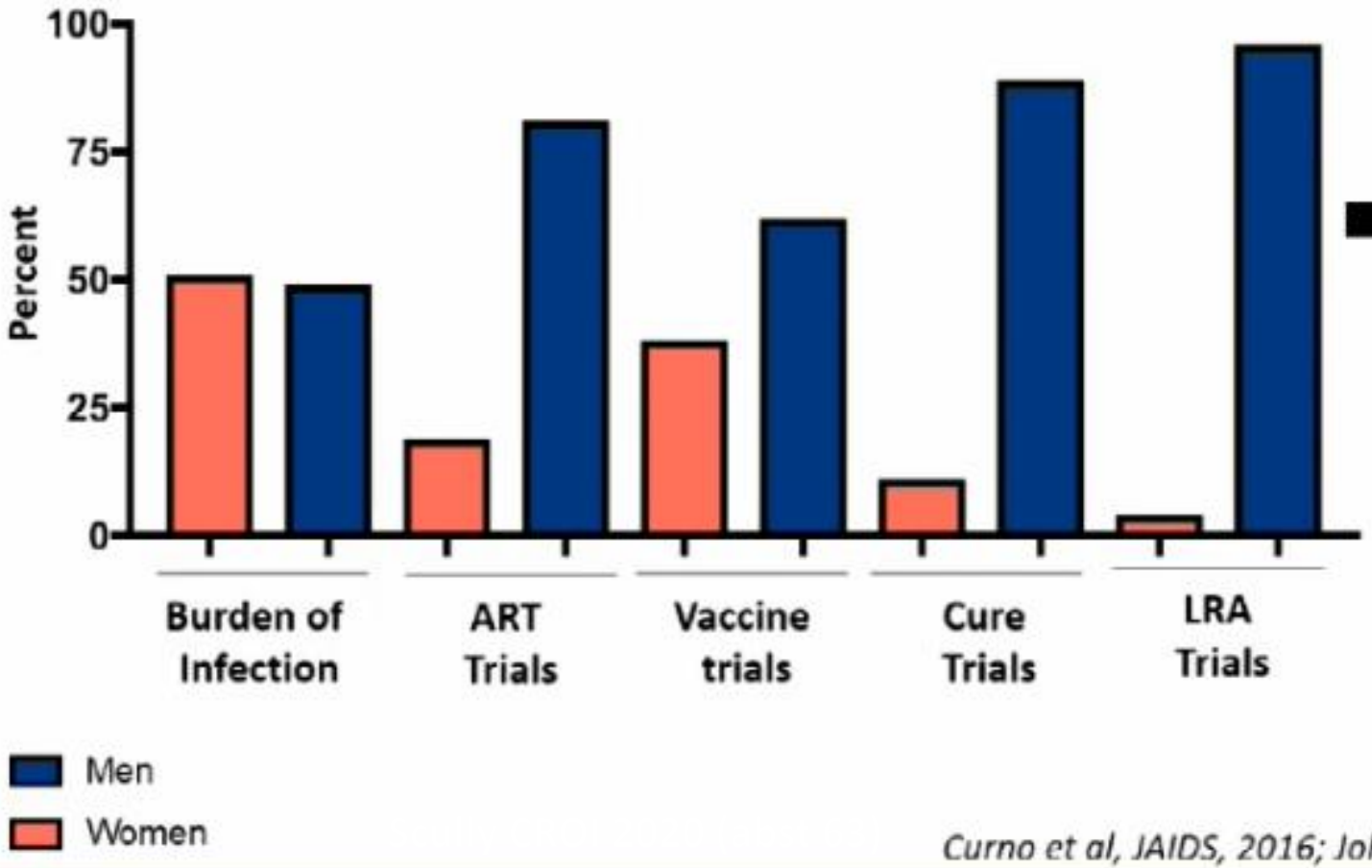
*Siedner et al, JID 2016;*
*Ticona et al., AIDS, 2015;*
*Mathad J et al., JAIDS 2016;*
*Hunt, P et al, Abstr 899 CROI 2015*

**Scully CROI 2020 (abst 63)**
*Son et al, Abstract 517 CROI, 2019*

# U=U : Definition



# Representation of women in HIV clinical trials




*Latency Reversal Agents update:*

263 participants
16 cisgender women
3 transgender women

**Scully CROI 2020 (abst 63)**

*Curno et al, JAIDS, 2016; Johnston and Heitzeg, AIDS Res Hum Retroviruses, 2015*

# IMPLEMENTATION OF U=U IN REAL LIFE IN ITALY: RESULTS FROM THE ICONA COHORT

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Giordano Madeddu[1], Andrea De Vito[1], Alessandro Cozzi-Lepri[2], Antonella Cingolani[3], Franco Maggiolo[4], Carlo Federico Perno[5], Roberta Gagliardini[6], Giulia Marchetti[5], Annalisa Saracino[7], Antonella D'Arminio Monforte[5], Andrea Antinori[6], Enrico Girardi[6] on behalf of Icona Foundation Study Group

[1]University of Sassari, Sassari, Italy, [2]University College London, London, UK, [3]Catholic University of the Sacred Heart, Rome, Italy, [4]Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy, [5]University of Milan, Milan, Italy, [6]Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy, [7]University of Bari, Bari, Italy.

- 8,241 PLWH were included in the study for a total of 12,670,888 PDFU. Median age was 39 (IQR 31,47), 20% were female. The majority of participants have acquired HIV infection trough sexual contacts (45.9% MSM and 38.5% heterosexuals). During follow-up 617 patients have spent ≤ 90% of the time with a VL ≤ 200 copies/ml, losing the U=U status.

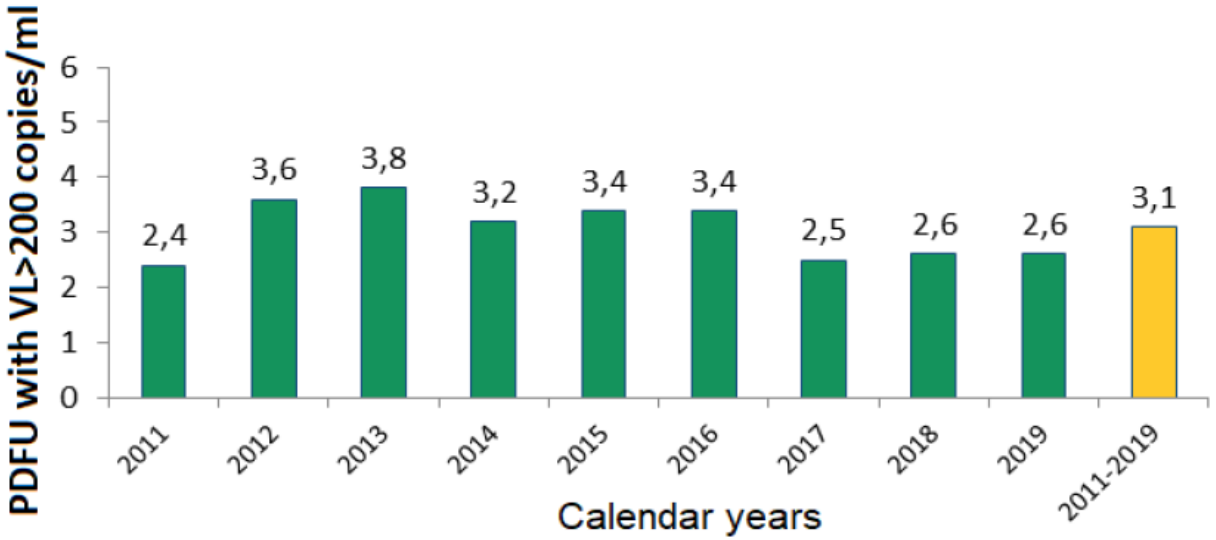



**Figure 2**. Person day follow up (PDFU) with VL >200 copies/ml by calendar year of follow-up.

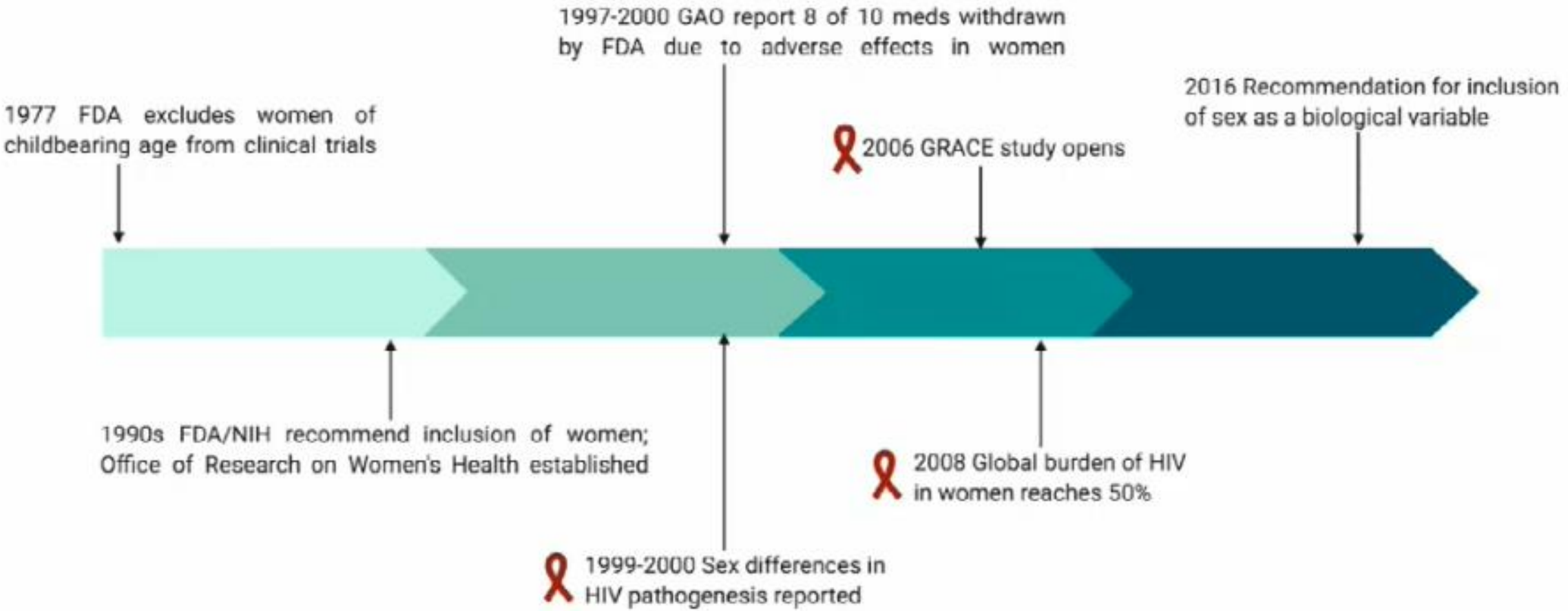
**Table 3.** Multivariate logistic regression estimates of factors associated with losing U=U status.

| | Unadjusted | | Adjusted* | | |
|---|---|---|---|---|---|
| Factor | Odds ratio (95% CI) | p-value | Odds ratio (95% CI) | p-value | Type III p-value |
| *Gender* | | | | | |
| Female vs. Male | 2.26 (1.89, 2.69) | <.001 | 1.55 (1.20, 2.00) | <.001 | |
| *Mode of HIV Transmission* | | | | | <.001 |
| PWID vs. MSM | 3.68 (2.86, 4.72) | <.001 | 2.50 (1.80, 3.46) | <.001 | |
| PWID vs. Heterosexual | 2.09 (1.72, 2.54) | <.001 | 1.43 (1.10, 1.87) | 0.009 | |
| PWID vs. Other/Unknown | 1.77 (1.24, 2.53) | 0.002 | 1.67 (1.07, 2.60) | 0.017 | |
| *Nationality* | | | | | |
| Foreign-born vs. Italian | 1.36 (1.14, 1.63) | <.001 | 1.42 (1.12, 1.80) | 0.004 | |
| *Employment, n (%)* | | | | | <.001 |
| Unemployed vs. Employed | 2.14 (1.70, 2.70) | <.001 | 1.46 (1.13, 1.89) | 0.004 | |
| *Previous virological failure, n* | | | | | <.001 |
| 1-3 vs. 0 | 2.02 (1.50, 2.73) | <.001 | 1.84 (1.22, 2.76) | 0.003 | |
| >3 vs. 0 | 3.52 (2.64, 4.69) | <.001 | 2.85 (1.84, 4.44) | <.001 | |

*Multivariable model includes all variables selected by backward selection that were retained with a p-value less than 0.3 level. Also adjusted for age, AIDS diagnosis, HBsAg/HCV status, duration of ART, anchor drug used, geographical region, diabetes, smoking, use of statins/lowering blood pressure drugs, glucose and prior STDs. PWID: people who inject drugs; MSM: men who have sex with men.

- ✓ Our population of PLWH meeting the definition of U=U at December 2010 maintained this status for 97% of the following 10 years of observation and the proportion showed a trend for a further increase in recent years.
- ✓ We also identified a small subset of **more fragile individuals, including <u>females</u>, PWID, unemployed and foreign-born, at higher risk of not maintaining the U=U status.**
- ✓ Taken together our results from a "real life" setting reinforce the validity of the U=U message in real world settings and the promotion of related campaigns

# Enrollment of women in clinical trials

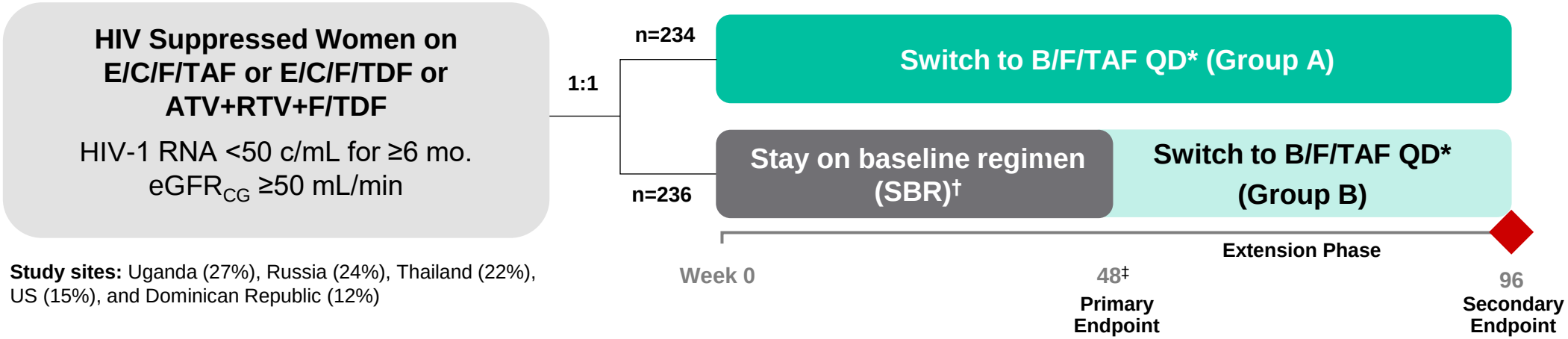



**Scully CROI 2020 (abst 63)**

# Study 1961: Suppressed Women Switched from E/C/F/TAF, E/C/F/TDF, or ATV+RTV+F/TDF

## Study Design

**Phase 3, multicenter, randomized, open-label, active-controlled study**




**Study sites:** Uganda (27%), Russia (24%), Thailand (22%), US (15%), and Dominican Republic (12%)

### Primary Endpoint

- HIV-1 RNA ≥50 copies/mL at Week 48 by FDA-defined snapshot algorithm (4% non-inferiority margin)

### Secondary Endpoint

- HIV-1 RNA ≥50 copies/mL at Week 96 for group A by M=E analysis
- HIV-1 RNA ≥50 copies/mL at Week 48 for group B by M=E analysis

*Given without regard to food; †Given with food; ‡at Week 48, participants had the option to receive B/F/TAF for an additional 48 weeks

ATV, atazanavir; E/C/F/TAF: elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; F, emtricitabine; RTV, ritonavir; TDF, tenofovir disoproxil fumarate.

**Kityo C, et al. IAS 2019. Mexico City, Mexico. Oral MOAB0106**

# Study 1961: Suppressed Women Switched from E/C/F/TAF, E/C/F/TDF, or ATV+RTV+F/TDF

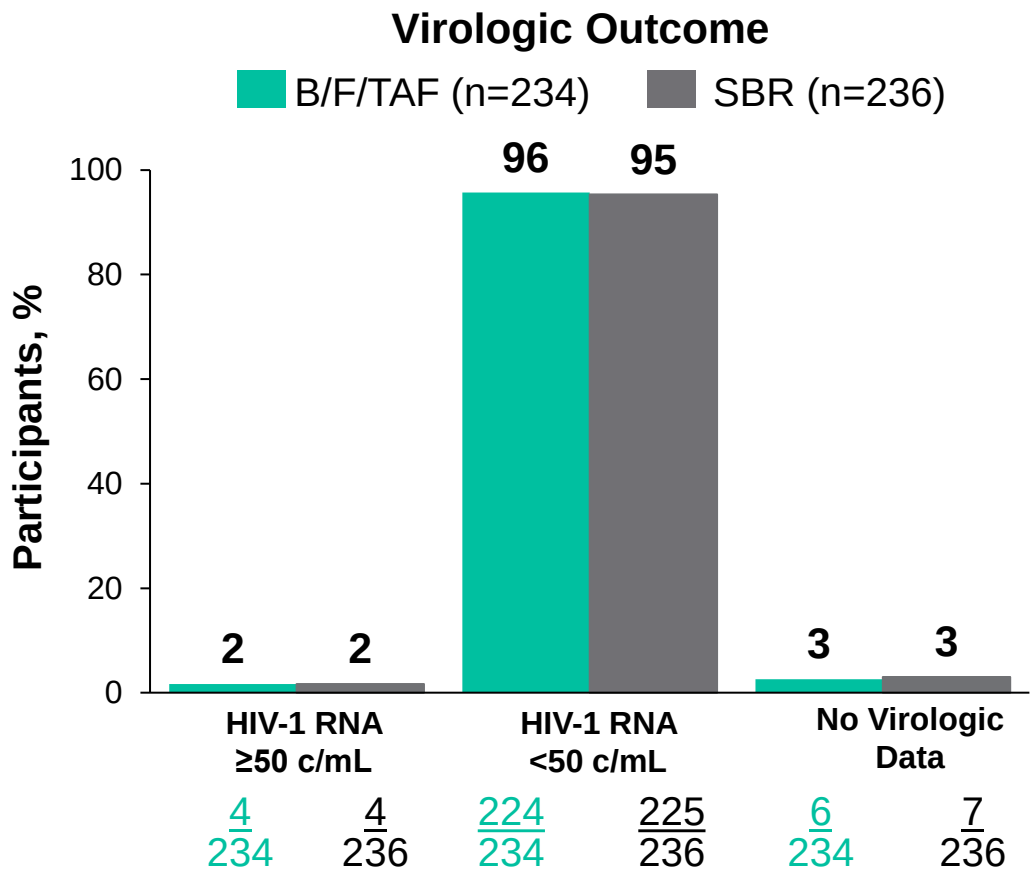
## Baseline Characteristics

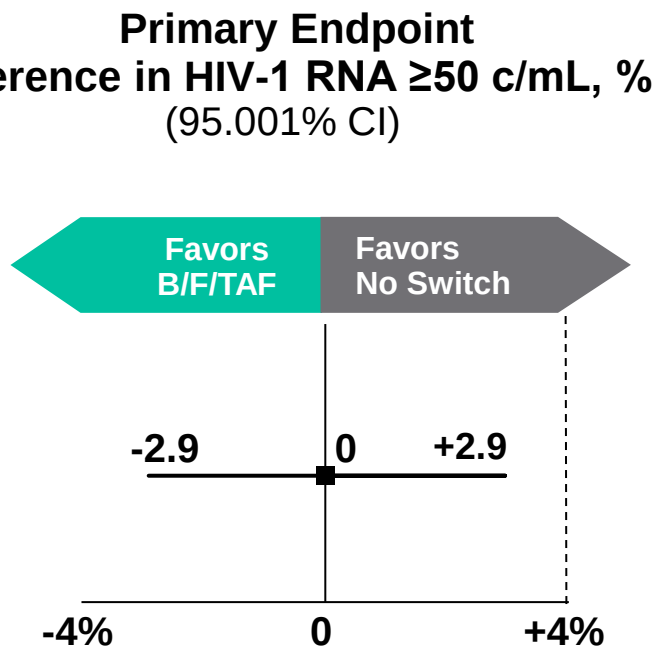
| | Group A B/F/TAF n=234 | Group B SBR to B/F/TAF n=228 |
|---|---|---|
| Age, median years (range) | 39 (21–63) | 41 (21–64) |
| Race/ethnicity, n (%) | | |
| Black or African descent | 91 (39) | 80 (35) |
| Asian | 48 (21) | 53 (23) |
| Hispanic/Latino ethnicity | 36 (15) | 35 (15) |
| CD4 cell count, median cells/µL (Q1, Q3) | 667 (532, 852) | 743 (554, 940) |
| CD4 count <200 cells/µL, n (%) | 1 (<1) | 0 |
| Estimated $GFR_{CG,}$ median mL/min (Q1, Q3) | 99.6 (82.8, 115.8) | 100.8 (83.4, 117.9) |
| Regimen at randomization | | |
| E/C/F/TAF | 124 (53) | 125 (53) |
| E/C/F/TDF | 99 (42) | 98 (42) |
| ATV + RTV + F/TDF | 11 (5) | 13 (6) |

Kityo C, et al. IAS 2019. Mexico City, Mexico. Oral MOAB0106

# Study 1961: Suppressed Women Switched from E/C/F/TAF, E/C/F/TDF, or ATV+RTV+F/TDF

## Virologic Outcome at Week 48 by FDA Snapshot Analysis




- Treatment outcomes between treatment groups were similar across age, race, and geographic region, and study drug adherence.[2]

**Switch to B/F/TAF had non-inferior efficacy vs SBR**
**No emergent resistance was detected in the B/F/TAF group***

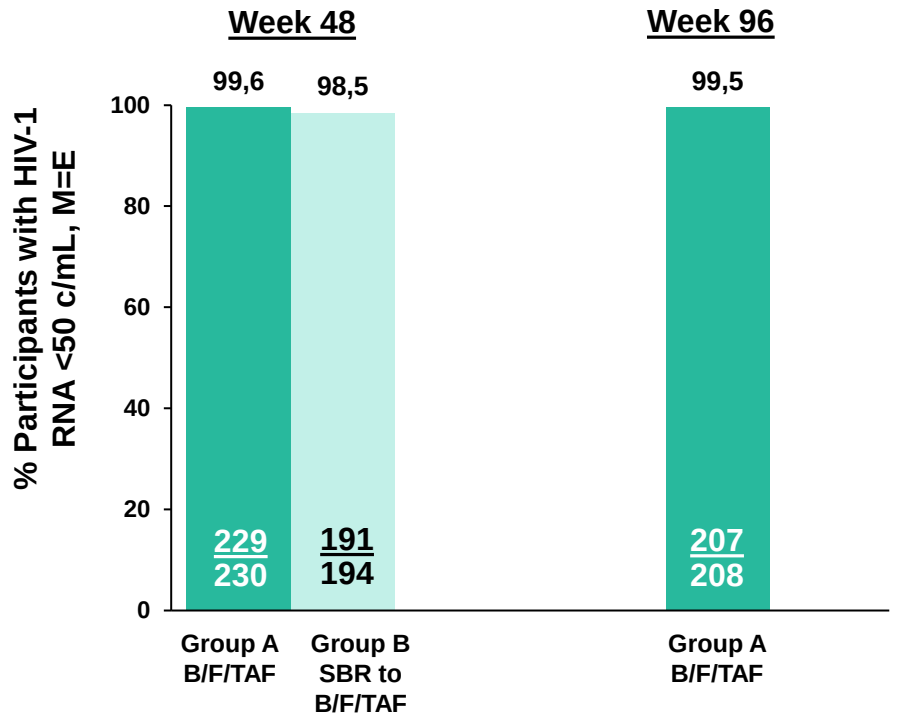
* 1 E/C/F/TAF participant developed emergent M184M/I/V mutation
SBR: Stayed on baseline regimen

Kityo C, et al. CROI 2018. Boston, MA. Poster 500

# Study 1961: Suppressed Women Switched from E/C/F/TAF, E/C/F/TDF, or ATV+RTV+F/TDF

## Efficacy and Resistance Analysis

**Virologic Outcomes (M=E Analysis)**




**Resistance Analysis Population and Resistance Summary**

| Resistance Category | B/F/TAF n=234 | SBR to B/F/TAF n=228 |
|---|---|---|
| Resistance Analysis Population | 1 (0.4%) | 3 (1.3%) |
| Emergent resistance | 0 | 0 |

- 1 participant developed M184M/I/V in the SBR group (E/C/F/TAF regimen) at Week 48 and subsequently resuppressed HIV-1 RNA after switching to B/F/TAF

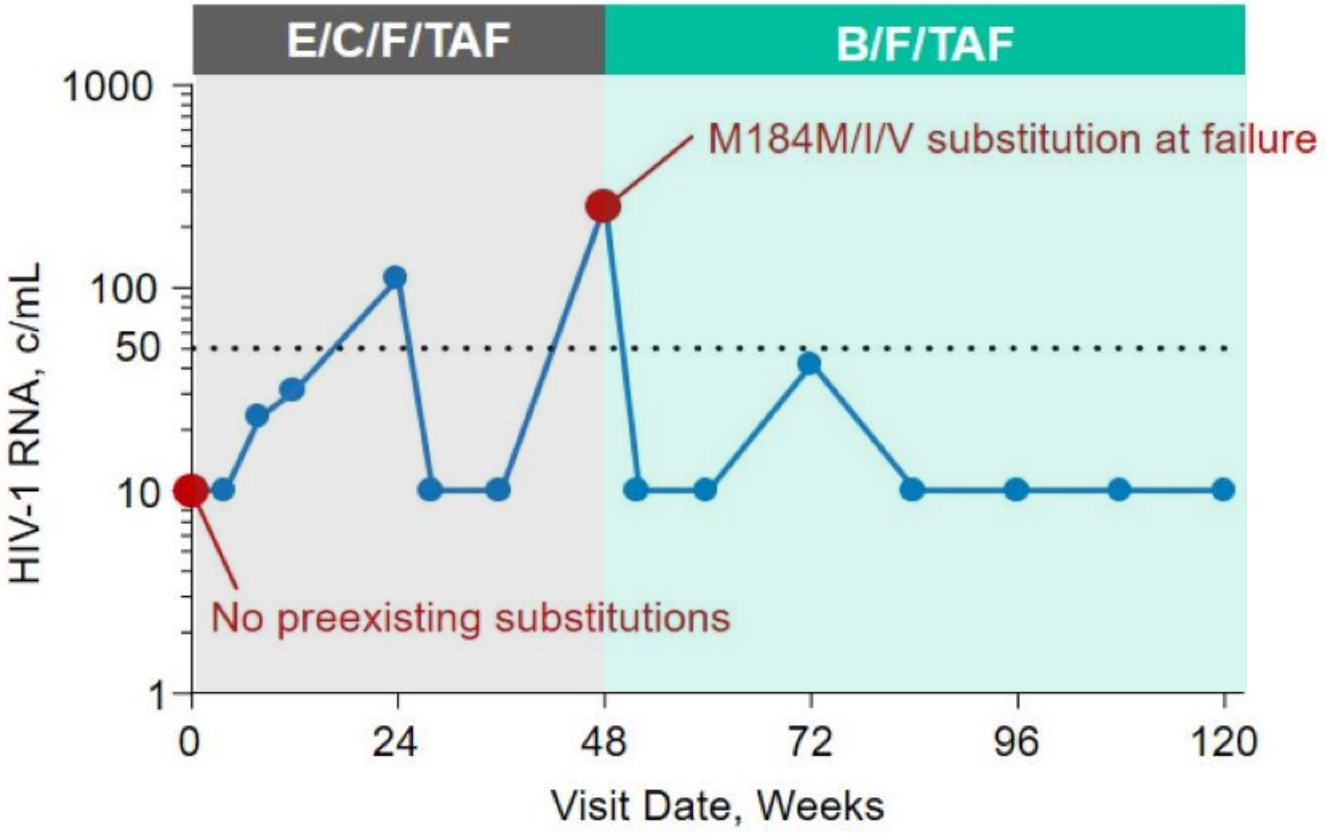
**Viral suppression rates remained high with no treatment-emergent resistance through 96 weeks**

FAS, full analysis set; R, resistance. FAS, full analysis set; R, resistance.

**Kityo C, et al. IAS 2019. Mexico City, Mexico. Oral MOAB0106**

# Study 1961: Suppressed Women Switched from E/C/F/TAF, E/C/F/TDF, or ATV+RTV+F/TDF

## M184V/I Isolate Suppressed Following Switch to B/F/TAF




- Patient with no pre-existing resistance mutation on E/C/F/TAF
- Virologic failure at Week 48 with 259c/mL
- Emergent M184V/I in RT
- Subsequently resuppressed when switched to B/F/TAF

Kityo C, et al. IAS 2019. Mexico City, Mexico. Oral MOAB0106

# Study 1961: Suppressed Women Switched from E/C/F/TAF, E/C/F/TDF, or ATV+RTV+F/TDF

## Safety through Week 96

### Adverse Events

| Participants, n (%) | | Group A B/F/TAF n=234 |
|---|---|---|
| **All grade** | | |
| **≥5%** | Upper respiratory tract infection | 29 (12) |
| | Nasopharyngitis | 28 (12) |
| | Headache | 25 (11) |
| | Urinary tract infection | 23 (10) |
| | Vulvovaginal candidiasis | 19 (8) |
| **Any Study drug-related AE** | | 23 (10) |
| **≥1%** | Iron deficiency anemia | 2 (1) |
| | Nausea | 2 (1) |
| | Vomiting | 2 (1) |
| | Headache | 2 (1) |
| | Dyslipidemia | 2 (1) |
| **Serious AE** | | 14 (6) |
| **AE leading to D/C or Death** | | 0 |

### Pregnancies

| Participants, n (%) | Groups A + B All B/F/TAF n=462 |
|---|---|
| D/C study drug due to pregnancy | 12 |
| Live birth | 7 |
| Fetal death | 1 (twins) |
| Elective termination | 2 |
| Pregnancy outcomes unknown | 2 |

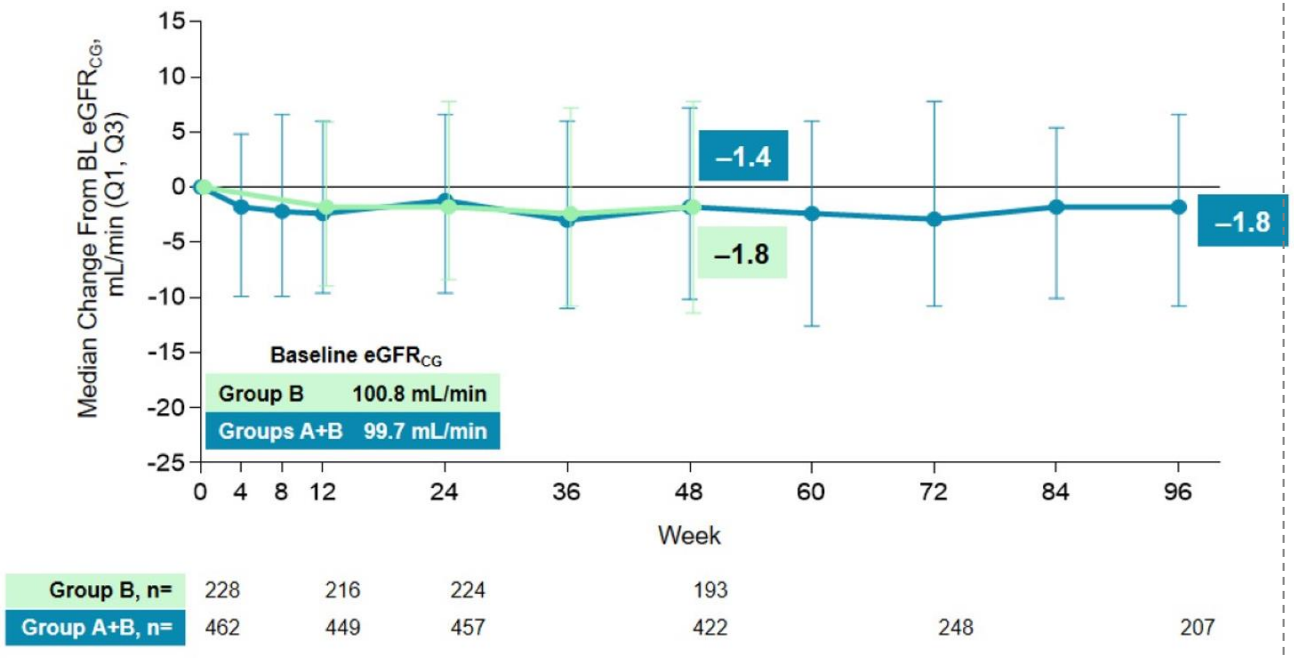
**B/F/TAF was well tolerated through week 96**

- Majority of AEs were Grade 1 or 2 in severity
- Grade 3 or 4 AE were low at <10%
  - No study drug-related AE was considered serious
- <1% discontinuation rate due to AEs
  - Group A: 0/234
  - Group B: 1/228 - Grade 2 ALT, AST, and GGT elevations

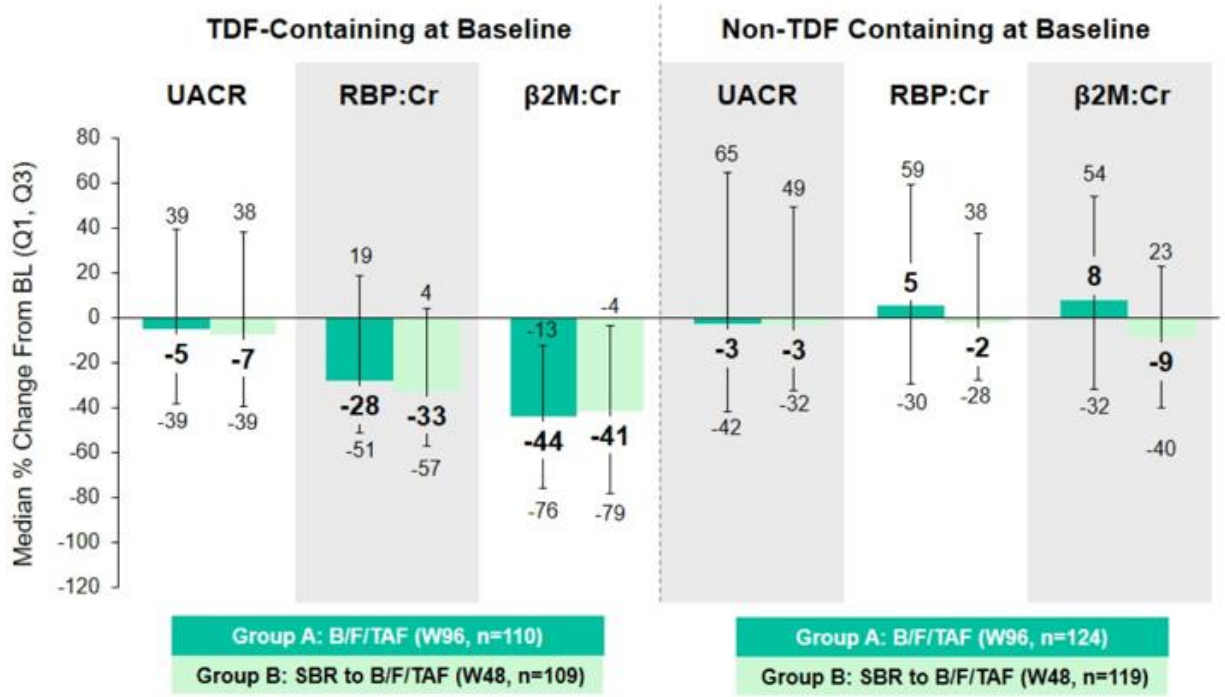
**Kityo C, et al. IAS 2019. Mexico City, Mexico. Oral MOAB0106**

# Changes in Renal Biomarkers at Week 96

**Changes in eGFR**




**Changes in Quantitative Proteinuria**




**Changes in eGFR were stable and similar to those observed in other Phase 3 studies**

**Improvements in renal tubular biomarkers when switched to B/F/TAF from TDF-containing regimens**

**No discontinuations due to renal AEs and no proximal tubulopathy in either B/F/TAF groups**

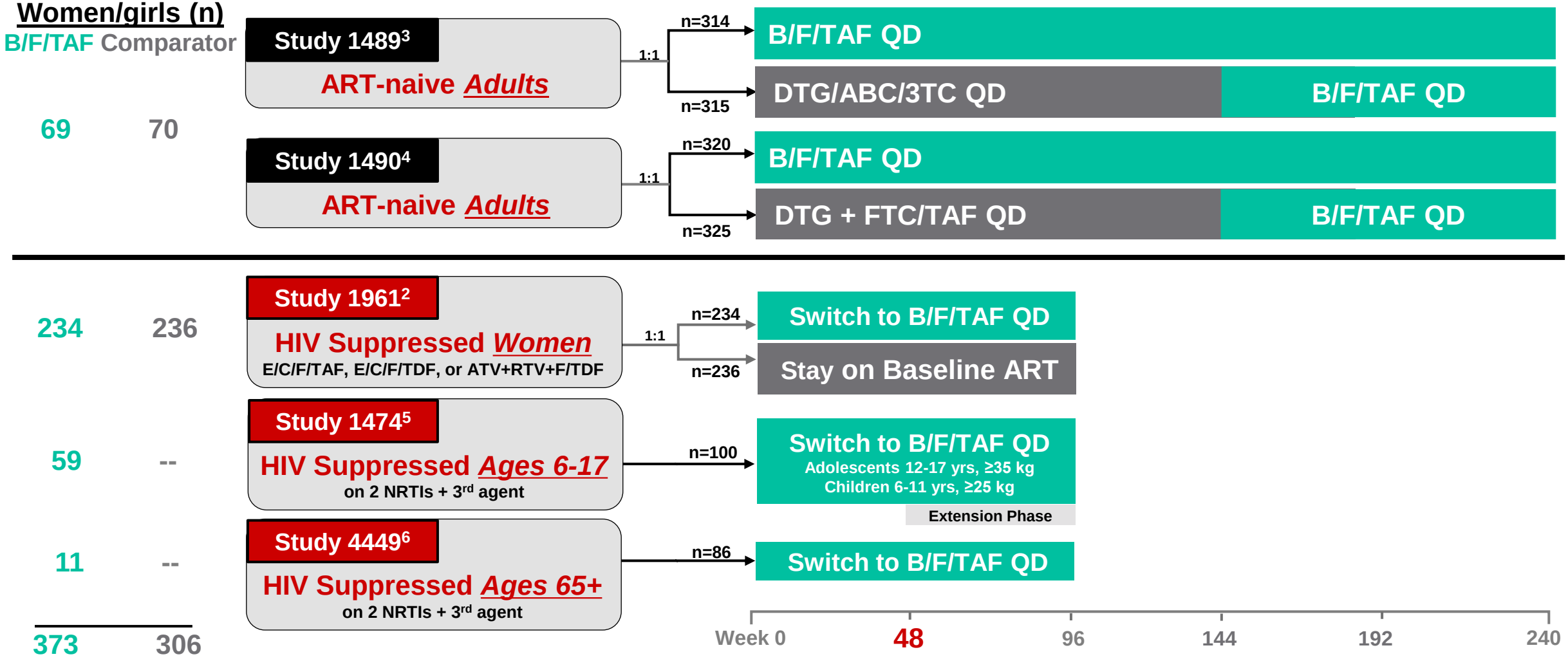
β2M, β2 microglobulin; Cr, creatinine; RBP, retinol-binding protein; UACR, urine albumin:Cr ratio.
* 53% baseline TAF and 47% baseline TDF

**Kityo C, et al. IAS 2019. Mexico City, Mexico. Oral MOAB0106**

# Five Clinical Trials: B/F/TAF in Women and Girls

## Study Design

Efficacy and safety of B/F/TAF vs comparators were assessed in 679 women and girls (sex at birth) across five phase 2 or 3 B/F/TAF clinical trials through 48 weeks



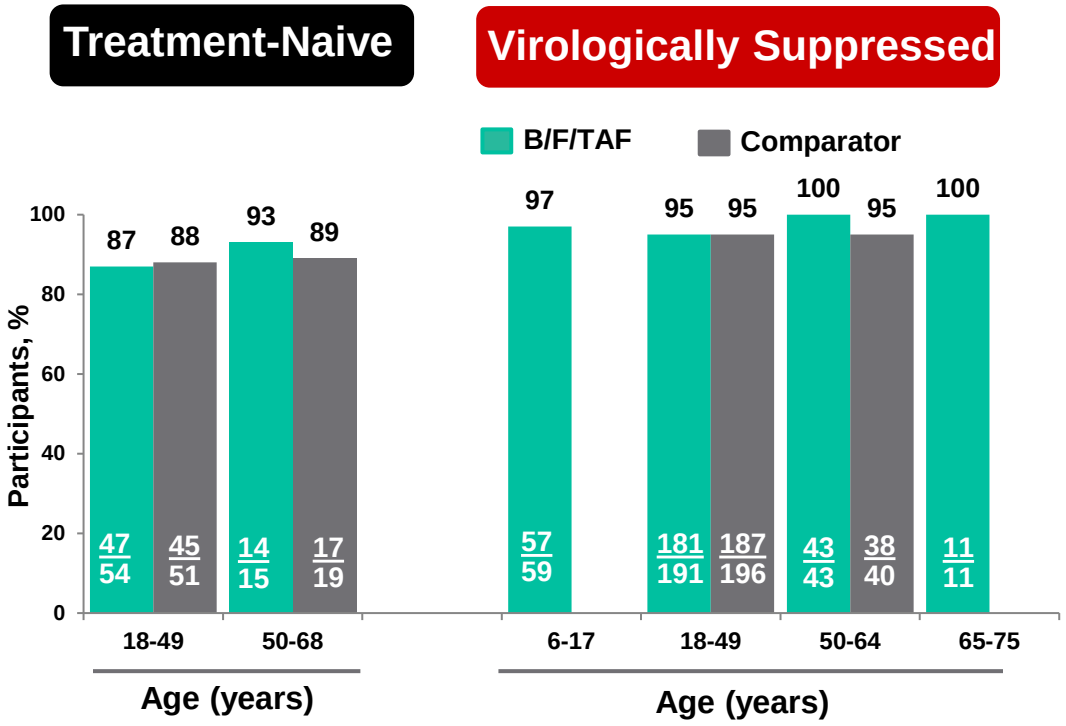

Orkin C, et al. EACS 2019. Basel, Switzerland. Oral PS7/6

*"B/F/TAF is indicated for the treatment of adults infected with human HIV-1; safety and efficacy in children under the age of 18 years have not yet been established"*

# Five Clinical Trials: B/F/TAF in Women and Girls

## Efficacy and Safety through Week 48

### Efficacy




- No B/F/TAF treatment-emergent resistance in women and girls through week 48

### Safety

| Age (years) | ART-Naïve | | Virologically Suppressed | | |
|---|---|---|---|---|---|
| | 18 - 49 n=54 | 50 - 68 n=15 | 6 - 17 n=59 | 18 - 49 n=191 | ≥50 n=54 |
| Any Grade AE | 85% | 80% | 78% | 63% | 80% |
| Study Drug-Related AEs | 19% | 7% | 14% | 9% | 6% |
| DC due to AE, n | 0 | 0 | 1* | 0 | 0 |

- Overall rates of Grade 3-4 AEs and serious AEs were low and similar to comparators
- Two fractures with B/F/TAF, both in VS >65 years and not considered study drug related
  1) Finger fracture
  2) Bilateral traumatic wrist fractures

**B/F/TAF was an effective and well-tolerated treatment for HIV infection with no resistance in women and girls through week 48**

* One girl with Grade 2 anxiety and insomnia

Orkin C, et al. EACS 2019. Basel, Switzerland. Oral PS7/6

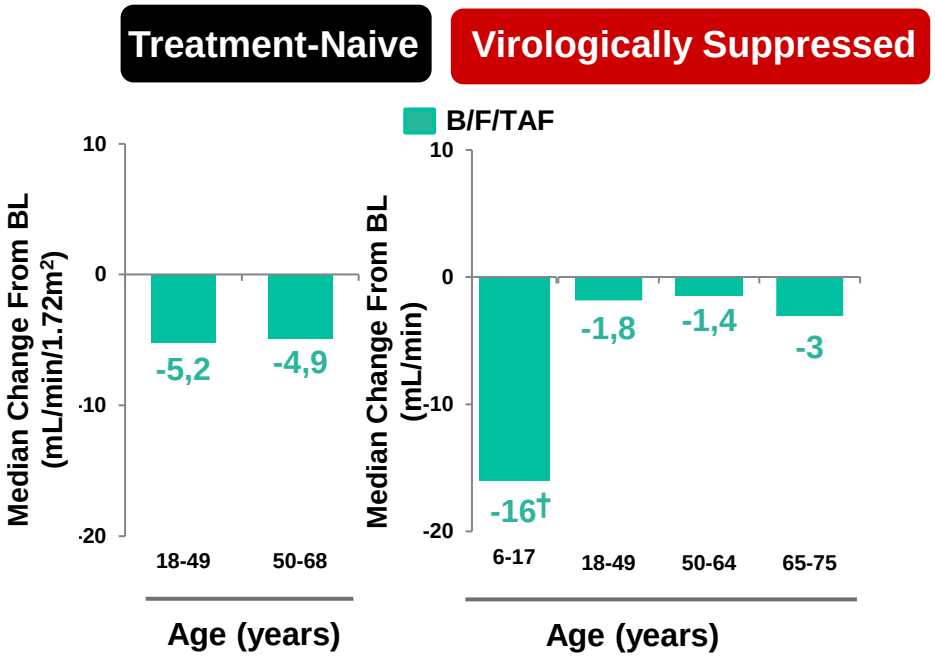


*"B/F/TAF is indicated for the treatment of adults infected with human HIV-1; safety and efficacy in children under the age of 18 years have not yet been established"*

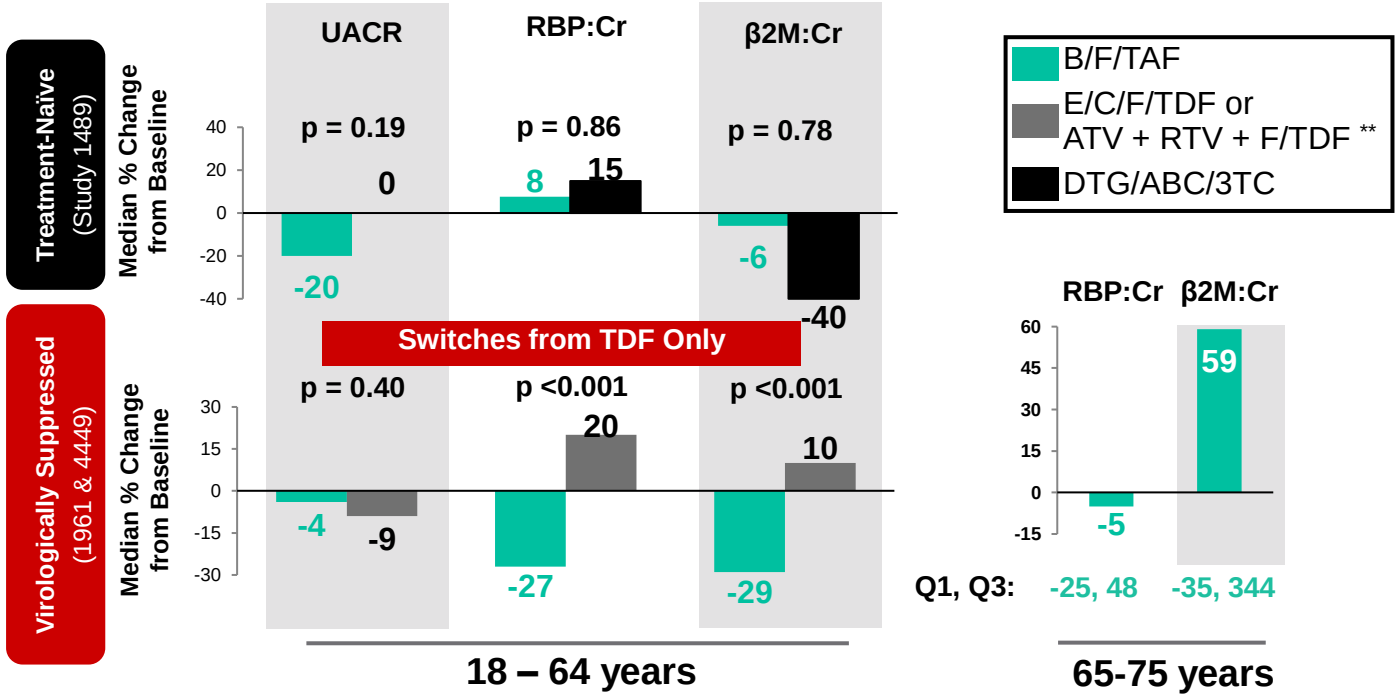
# Five Clinical Trials: B/F/TAF in Women and Girls

## Renal Safety in Women and Girls at Week 48

### eGFR*




### Renal Biomarkers‡



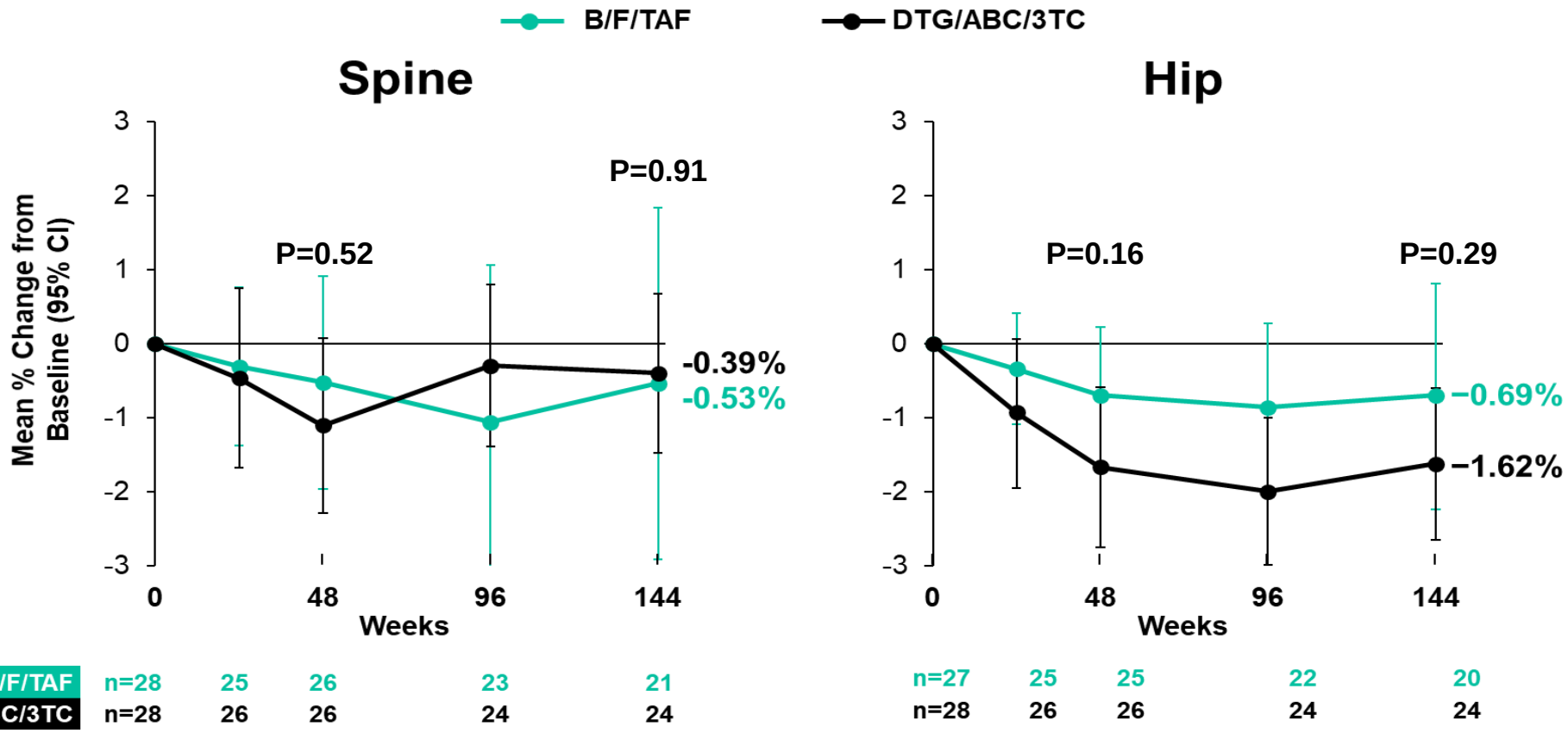

**Small changes from baseline in eGFR were observed, with no effect on actual GFR and no cases of Fanconi syndrome or proximal renal tubulopathy in women and girls**

* eGFR calculated using Schwartz formula for pediatrics and Cockcroft-Gault for adults
† Week 48 median eGFR was 133 mL/min/1.72m$^2$ in the pediatric population
‡ In pediatric Study 1474 renal tubular biomarkers were not required by the FDA. In Study 4449 4/8 women with urinary protein to creatinine ratio (UACR) > 200 mg/g improved to <200 mg/g at W48
** 48% of the overall Study 1961 population had baseline TDF-based regimen: E/C/F/TDF (42%) and ATV+RTV+FTC/TDF (6%)

Orkin C, et al. EACS 2019. Basel, Switzerland. Oral PS7/6

# Study 1489: B/F/TAF vs DTG/ABC/3TC in ART-Naïve Women

## Bone Safety in Women through Week 144




**Changes from baseline in BMD were comparable between B/F/TAF vs DTG/ABC/3TC in treatment-naïve women**

BMD, bone mineral density

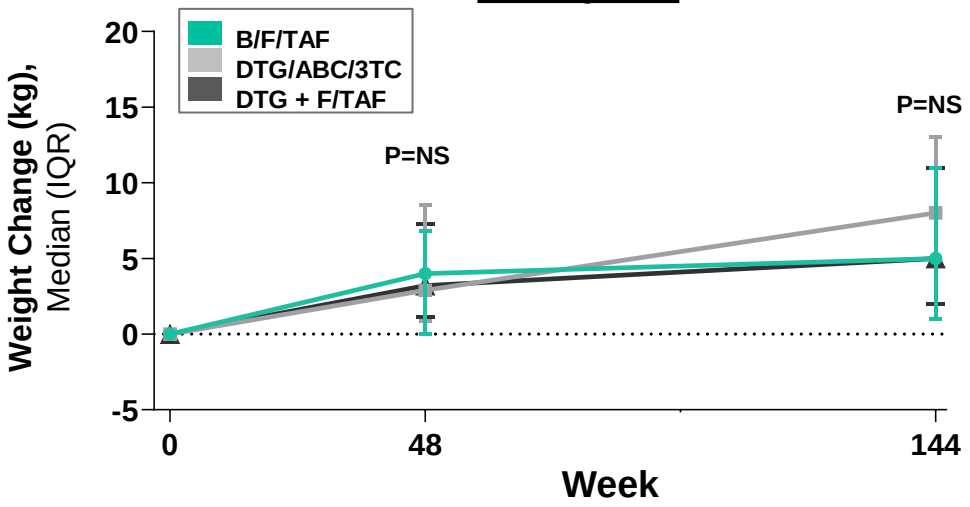
Orkin C, et al. EACS 2019. Basel, Switzerland. Oral PS7/6

# Five Clinical Trials: B/F/TAF in Women and Girls

## Weight Change from Baseline in Women through Weeks 48 & 144*

**Treatment-Naive**

**18-68 years**

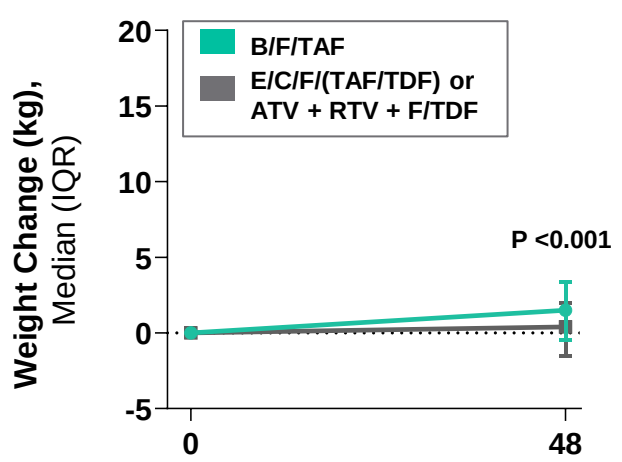



| | B/F/TAF | Comparators | |
|---|---|---|---|
| Sample size (n): | 63 | 30 | 32 |
| Baseline median weight (kg): | 74 | 84 | 70 |
| Median change (kg) | 4.0 | 2.9 | 3.2 |

| | B/F/TAF | Comparators | |
|---|---|---|---|
| Sample size (n): | 50 | 29 | 29 |
| Baseline median weight (kg): | 74 | 84 | 70 |
| Median change (kg) | 5.0 | 7.9 | 4.9 |

**Virologically Suppressed**

**18-64 years**




| | B/F/TAF | Comparators |
|---|---|---|
| Sample size (n): | 229 | 230 |
| Baseline median weight (kg): | 67 | 68 |
| Median change (kg) | 1.5 | 0.4 |

**Weight changes from baseline to W144 were comparable between B/F/TAF and comparators in ART-naïve women; with small differences (<1.5 kg)* in virologically suppressed women through W48**

IQR, interquartile range. P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment group
* Differences in mean, median, maximum, Q1 and Q3 values: < 1.5 kg for virologically suppressed and < 2.0 kg for ART-naive

Orkin C, et al. EACS 2019. Basel, Switzerland. Oral PS7/6

# IAS-USA and DHHS Perinatal Guidelines

## Recommendations for Triple Therapy Initiation in Pregnancy

| | DHHS PERINATAL 2018[1] | IAS-USA 2018[2] |
|---|---|---|
| **Drug Class** | **Preferred Initial Combination Regimens For ARV-Naïve Pregnant Women** | **Generally Recommended Initial Regimens In Pregnancy** |
| **INSTI** | RAL*<br>DTG **after 1st trimester**† | RAL |
| **NRTI** | ABC§/3TC or TDF/FTC or TDF/3TC | ABC*/3TC (or FTC) or<br>TDF/FTC (or 3TC) |
| **PI** | ATV/r<br>DRV/r | ATV/r<br>DRV/r twice daily |

***Twice daily dosing is required**
**† † 1st trimester = less than 14 weeks [up to 13 6/7 weeks] gestational age by last menstrual period**
**§ Only for HLA-B*5701 negative**

**1. DHHS Perinatal Guidelines. Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States. December 2018**
**2. Saag M, et al. JAMA 2018;320(4):379-396. https://www.iasusa.org/guidelines**

# DHHS Perinatal Guidelines

## Recommendations for INSTI-Based STRs in Pregnant Women

| | B/F/TAF | E/C/F/TAF | DTG/ABC/3TC |
|---|---|---|---|
| **Integrase Inhibitor** | **BIC** | **EVG/COBI** | **DTG** |
| | ▪ Insufficient data | ▪ In a person who is pregnant, EVG/COBI **is also not recommended** because lower EVG/COBI concentrations have been reported when this drug is given during the second and third trimesters. | ▪ May use in 2nd & 3rd trimesters<br>▪ Desire pregnancy or not using effective contraception: **do not initiate DTG**[2]<br>▪ No desire of pregnancy & using effective contraception:[2]<br>– DTG can be considered; pregnancy test prior to DTG initiation; discuss potential of DTG to fetus and effective use of contraception |
| **NRTI Backbone** | **TAF/FTC**<br>***Insufficient Data in Pregnancy to Recommend Routine Use*** | **TAF/FTC**<br>***Insufficient Data in Pregnancy to Recommend Routine Use*** | **ABC/3TC**<br>***Preferred*** |
| | ▪ Insufficient data on use of TAF in pregnancy | ▪ Insufficient data on use of TAF in pregnancy | ▪ ABC **should not be used** in patients who test + for HLA-B*5701 because of risk of hypersensitivity reaction |

**DHHS Perinatal Guidelines. Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States. December 2018**

# Conclusioni

- Nonostante gli indubbi progressi compiuti in termini di sopravvivenza, rimane ancora molto da investigare in merito alla storia naturale e alla patogenesi dell'infezione da HIV nella donna

- Sono necessari ulteriori dati sulle nuove molecole in considerazione delle variabilità legate al sesso e alle peculiarità della gestione della terapia antiretrovirale nella donna in età fertile e in gravidanza

- Da quanto emerso dall'analisi dei trials clinici le nuove STR contenenti Bictegravir appaiono efficaci e sicure nelle donne con HIV