Parametri di scelta della terapia antiretrovirale nel genere femminile

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OSPEDALI DEI COLLI
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OUTLINE

- Linee guida
- Perché:
  - Comorbidità
  - Weight gain
  - Gravidanza e PK/safety
- Clinical trials: a never ending story

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SIMIT
Società Italiana di Malattie Infettive e Tropicali

In collaborazione con:

Ministero della Salute

Sezioni L e M del Comitato Tecnico Sanitario

SEZIONE 4
Popolazioni cui porre attenzione

DONNA

Nel mondo il 51% delle persone con infezione da HIV appartiene al genere femminile. In Italia, nel 2016 sono state registrate 796 nuove diagnosi di infezione da HIV, pari al 23,1% di tutte le nuove segnalazioni, in donne con età mediana di 36 anni e di cui 61,3% di nazionalità non italiana, dato in aumento rispetto agli anni precedenti. Inoltre su 778 nuovi casi di AIDS, 183 sono stati registrati in donne, il 50% delle quali con età ≥ 40 [1]. Nella maggior parte dei casi il virus è stato contratto attraverso rapporti eterosessuali, spesso con il proprio partner stabile. Non esistono differenze di genere nella risposta alla terapia antiretrovirale, anche se in una recente analisi le donne con età >65 anni hanno evidenziato una peggior risposta virologica rispetto al genere maschile [2]. Inoltre vi sono differenze di genere e di etnia che penalizzano il sesso femminile per quanto riguarda le condizioni culturali, socio-economiche, l'accesso alle cure, gli effetti collaterali con conseguente riduzione dell'aderenza e maggiori tassi di interruzione della terapia [3]. E' dimostrato come una terapia completa a formulazione compatta (1 compressa) sia garanzia di aderenza e di risposta virologica nella popolazione femminile, considerata classicamente "difficile" [4,5]. Nel percorso assistenziale della donna con infezione da HIV è pertanto necessario considerare alcuni principali elementi quali: 1) Le peculiarità della ART (Tab. 1); La tossicità e la comorbosità (Tab. 2); La prevenzione primaria (Tab. 3).

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Linee Guida Italiane sull'utilizzo della Terapia Antiretrovirale e la gestione diagnostico-clinica delle persone con infezione da HIV-1

Edizione 2017

Tabella 1 - La terapia antiretrovirale nella donna HIV positiva.

AZIONI	RACCOMANDAZIONE (FORZA/EVIDENZA)	RIFERIMENTO BIBLIOGRAFICO
Non vi sono differenze significative con la popolazione maschile per quanto riguarda l'inizio della terapia antiretrovirale, la risposta virologica ed immunologica.	[AI]	[6-7]
Attenzione particolare va posta alle donne con età >65 anni che hanno dimostrato una risposta virologica inferiore rispetto al genere maschile.	[BII]	[2]
Nelle donne naïve alla terapia antiretrovirale considerare la preferenza di regimi STR con il fine di garantire l'aderenza e la risposta virologica .	[AI]	[4-5]
Nelle donne naïve alla ART, con desiderio di genitorialità o sessualmente attive e che non utilizzano mezzi contraccettivi non utilizzare regimi che contengono Efavirenz per il rischio teratogeno nel 1° trimestre di gravidanza come pure l'uso di cobicistat e TAF per i dati ancora limitati. Tra gli inibitori dell'integrasi, raltegravir è attualmente il farmaco raccomandato in gravidanza.	[AIII] [AII]	[8-9] [10]
Considerare di mantenere efavirenz nel regime antiretrovirale se la gravidanza viene identificata dopo l' 8° settimana di gestazione.	[BII]	[11]
Anche se il loro utilizzo non è più raccomandato, nella donna deve essere tenuto presente il rischio di epatotossicità da NVP e di acidosi lattica da AZT	[AIII]	[12-13]
Considerare regimi con inibitori delle integrasi nella donne che assumono contraccettivi orali per l'assenza di interazioni farmacologiche	[AII]	[14-15]
Considerare di implementare i programmi di accesso al test, specie nelle donne straniere, e di *mantenimento in cura* per favorire l'aderenza specialmente in donne giovani adulte (<24 anni)	[BIII]	[16-17]

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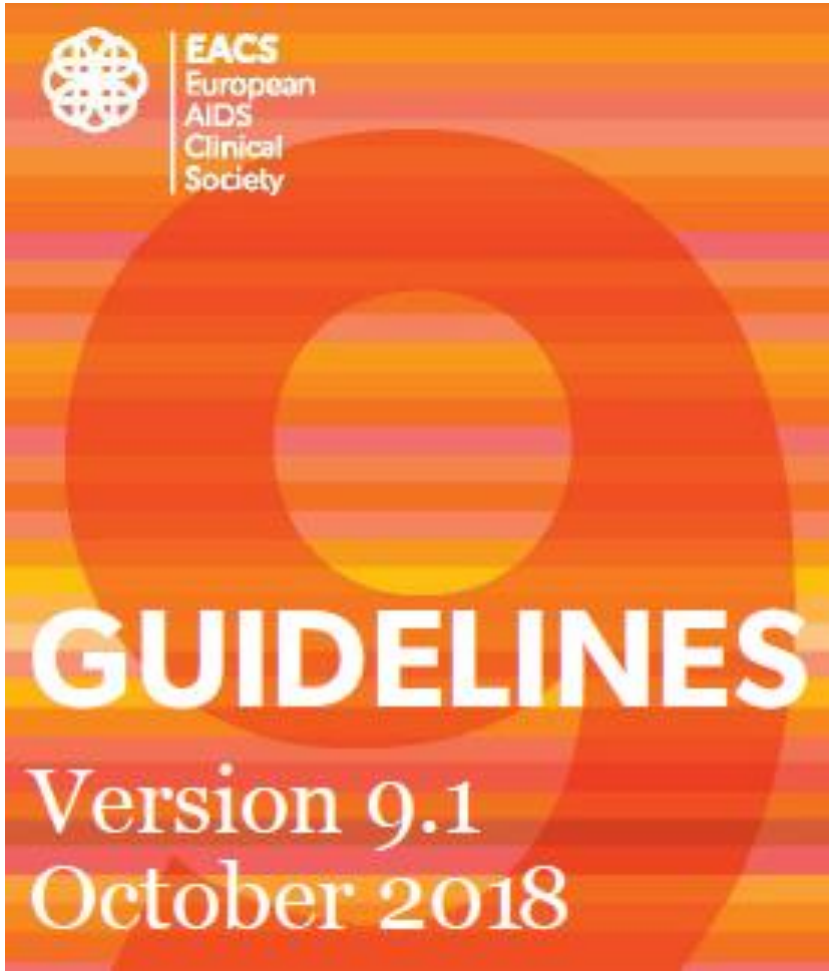
Edizione 2017

Tabella 2 – La tossicità e la comorbosità nella donna HIV positiva.

AZIONI	RACCOMANDAZIONE (FORZA/EVIDENZA)	RIFERIMENTO BIBLIOGRAFICO
Iniziare una cART che tenga conto dei potenziali effetti collaterali e tossicità, delle comorbidità e della *convenience* del regime in modo da ridurre il rischio di sospensione o mancata aderenza.	[AII]	[18-20]
La funzionalità renale risulta essere più compromessa nella donna. Eseguire il calcolo della Cl creatinina ed esame urine in tutte le donne al momento della diagnosi, prima dell'inizio della terapia e ai controlli annuali; qualora si utilizzino farmaci potenzialmente nefrotossici il controllo deve essere eseguito semestralmente.	[AII] [BII]	[21]
Rispetto alla popolazione generale femminile, analizzando fattori quali menopausa e peso, le donne HIV+ risultano essere a maggior rischio di bassi livelli di densità minerale ossea (BMD) e vitamina D. Controllare la BMD con Densitometria assiale a Raggi X (DEXA), dosaggio vitamina D e PTH in tutte le donne sia naïve che in terapia antiretrovirale, in menopausa e premenopausa con più di un fattore di	[AI] [AI]	[22-23]
rischio comuni per osteoporosi. Utilizzare i marcatori di turnover osseo (p.e. N-telopeptide ed osteocalcina) ed eventuali algoritmi per predire il rischio di frattura, integrare il dato sensitometrico e monitorare l'andamento dell'osteopenia/osteoporosi	[BI] [AII]	[23]
In considerazione dell'elevato rischio di osteopenia/osteoporosi e/o problemi renali la terapia antiretrovirale dovrebbe contenere TAF o altri regimi alternativi non contenenti TDF	[AII]	[24-25]
Il trattamento dell'epatite cronica HCV correlata con i nuovi farmaci antivirali diretti (DAAs) deve essere effettuato il prima possibile, indipendentemente dal grado della malattia epatica, in modo da evitare il periodo della menopausa che è stato dimostrato accompagnarsi ad una più rapida progressione della fibrosi epatica.	[AI] [CIII]	[26] [27]

Tabella 3 – La prevenzione primaria nella donna con HIV

AZIONI	RACCOMANDAZIONE (FORZA/EVIDENZA)	RIFERIMENTO BIBLIOGRAFICO
E' raccomandata la valutazione dello stato menopausale in tutte le donne al primo accesso e successivamente al fine di ottimizzare i percorsi di diagnosi e cura. Le donne con infezione da HIV rispetto alle sieronegative sono a maggior rischio di menopausa precoce e la menopausa stessa può influenzare negativamente il decorso dell'infezione da HIV.	[AI]	[28]
Le donne con HIV mostrano un rischio elevato di sviluppare depressione. Lo screening per la depressione dovrebbe essere inserito tra gli esami di routine soprattutto per la paziente con segni e sintomi di pre o menopausa; programmare interventi di presa in cura della paziente affetta da depressione. Regimi alternativi a efavirenz devono essere considerati nella donna con depressione.	[AII] [AII] [AII]	[29] [30]
Nella donna HIV il rischio di patologie neoplastiche è simile a quella della popolazione generale: la prevenzione e la diagnosi delle patologie tumorali devono riguardare tutte le neoplasie non solo quelle HIV correlate. Eseguire lo screening per il carcinoma della cervice uterina, se possibile con ricerca e genotipizzazione di HPV, in tutte le donne HIV. Nelle donne fino al compimento del 45° anno di età, è raccomandata la vaccinazione per HPV prediligendo dove possibile la vaccinazione nono-valente. Per tutte le ulteriori indicazioni fare riferimento alla sezione "Tumori".	[AI] [AI] [AI]	[31] [32-33]
In considerazione dell'aumentato rischio di ascessi tubo-ovarici, infiammazione pelvica con possibile occlusione tubarica bilaterale e relativa infertilità, si raccomanda uno screening per *Clamydia* e *Mycoplasma*.	[AII]	[34]
E' raccomandata la valutazione del rischio sessuale, la diagnosi e la cura delle infezioni genitali per ridurre il rischio di acquisizione delle altre patologie sessualmente trasmesse.	[AI]	[35]
Per le coppie siero discordanti con desiderio di genitorialità è raccomandato un adeguato *counselling* che valuti caso per caso, interventi personalizzati includenti lo screening e il trattamento delle malattie a trasmissione sessuale, l'uso della cART al fine di sopprimere la viremia HIV nel partner infetto, l'uso della profilassi pre-esposizione nel partner HIV-negativo nel caso in cui non si riesca ad affrontare con serenità un concepimento per via naturale.	[BII]	[36-37]



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AIDSinfo

Women with HIV (Last updated October 25, 2018; last reviewed October 25, 2018)

Solo di gravidanza!

Panel's Recommendations

- Antiretroviral therapy (ART) is recommended for all persons living with HIV to improve their health and to reduce the risk of HIV transmission to sex partners without HIV (**AI**).
- When prescribing antiretroviral (ARV) drugs, clinicians should take into account that some ARV drugs have significant pharmacokinetic (PK) interactions with hormonal contraceptives; an alternative or additional effective contraceptive method to prevent unplanned pregnancy is recommended (**AIII**). Switching to an ARV drug without interactions with hormonal contraceptives may also be considered (**BIII**).
- A pregnancy test should be performed for those of childbearing potential prior to initiation of ART (**AIII**).
- Preliminary data suggest there may be an increased risk of neural tube defects (NTD) in infants born to women who were receiving dolutegravir (DTG) at the time of conception. Until more information is available, DTG **is not recommended** for use in individuals who are pregnant and within 12 weeks post-conception and those who are contemplating pregnancy, unless there are no alternative options (**AII**).
- Providers should discuss the potential risks and benefits of DTG with individuals of childbearing potential and provide appropriate counseling so that the individual can make an informed decision. For those who are sexually active and not using effective contraception, choosing an alternative to DTG is recommended. For those who are using effective contraception, use of a DTG-based regimen is reasonable after discussing the risks and benefits with the individual.
- Individuals who become pregnant and present for antenatal care at 12 weeks post-conception or later may initiate or continue DTG-based regimens (**CIII**).
- In a patient with multidrug-resistant HIV who has no alternatives to DTG, the decision of whether to use DTG should be made after careful consideration of the risk of NTDs in the infant if pregnancy occurs while a patient is taking DTG, and the risks of persistent viremia in the patient and potential HIV transmission to the fetus if pregnancy occurs while the patient is not on effective ART.
- During pregnancy, an additional goal of ART is to maintain a viral load below the limit of detection throughout pregnancy to reduce the risk of transmission to the fetus and newborn (**AI**).
- When selecting an ARV combination regimen for a pregnant woman, clinicians should consider the available safety, efficacy, and PK data on use during pregnancy for each agent. The risks and benefits of ARV use during pregnancy should be discussed with all individuals of childbearing potential (**AIII**) and clinicians should consult the most current Perinatal Guidelines when designing a regimen (**AIII**).

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

OUTLINE

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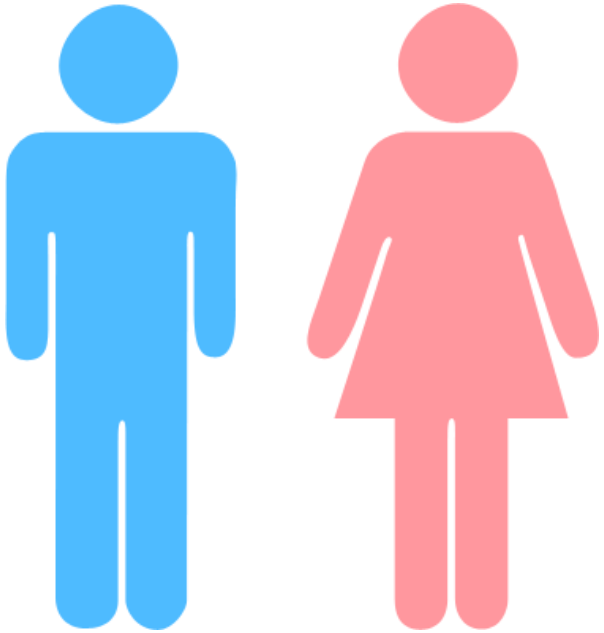
Differences between women and men in:



- Physiology
- Body dysmorphia
- Weight distribution
- Pharmacokinetics

- Historically, most ART trials conducted in men
- Women constituted 19.2% of participants in systematic review of ART trials
  - Likely owing to entry criteria precluding birth control, pregnancy, breastfeeding
- Phase III data emerging from studies of modern ART regimens in women: GRACE, WAVES, ARIA, etc…

Curno MJ, et al. J Acquir Immune Defic Syndr. 2016;71:181-188.

Women Facing HIV. Key Question on Women with HIV Infection: Italian Consensus Workshop

G. Carosi, P. Nasta, S. Fiore, A. Matteelli, R. Cauda, E. Ferrazzi, E. Tamburrini, V. Savasi, T. Bini, M. Ravizza, A. Bucceri, F. Vichi, R. Murri, F. Mazzotta, A. d'Arminio Monforte, on behalf of the members of the Italian Working Group for the Women with HIV Management Guidelines

Infection 37 · 2009 · No. 2

Women and HAART (Key Question 1)

Although mortality has significantly decreased among people with HIV/AIDS due to the availability of HAART [4, 5], according to several authors the gain in disease-free survival time has been considerably less among women than in men [5, 6]. In a context of global decrease since 2000, AIDS-related deaths have been more frequent in women than in men, even in a setting of universal access to care by HIV-infected women [7]. There are several possible explanations for this finding, including sex differences in the initiation of HAART regimens [8], antiretroviral (ARV)-associated adverse events and adherence to complex or poorly tolerated regimens [9]. The expert panel of the consensus workshop, focusing

- **L'intervallo di sopravvivenza libero da malattia è più breve.**
- **La morte per eventi AIDS-definenti è più frequente.**

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Women show lower HIV RNA plasma levels than men—at a given duration of HIV infection and at a given CD4 count [12, 13]. Estradiol and progesterone are reported to regulate HIV-1 replication, lowering the HIV-1 long terminal repeat (LTR) [14]. Once therapy is initiated, no gender differences in immuno–virological and clinical outcome are recorded [15]. However, in several reports there is some evidence for a better immuno–virological response to treatment in women relative to men [16]. Nevertheless, there is no apparent difference in response to therapy, clinical progression and survival according to sex in treated individuals [17, 18]. To date, no specific recommendations on the different time of therapy initiation appear to be necessary (**B-II**).

- **Le donne presentano livelli di HIV RNA più bassi .**
- **Estradiolo e progesterone agiscono su HIV-1 long term repeat (LTR), riducendone l'espressione e regolando la replicazione virale.**

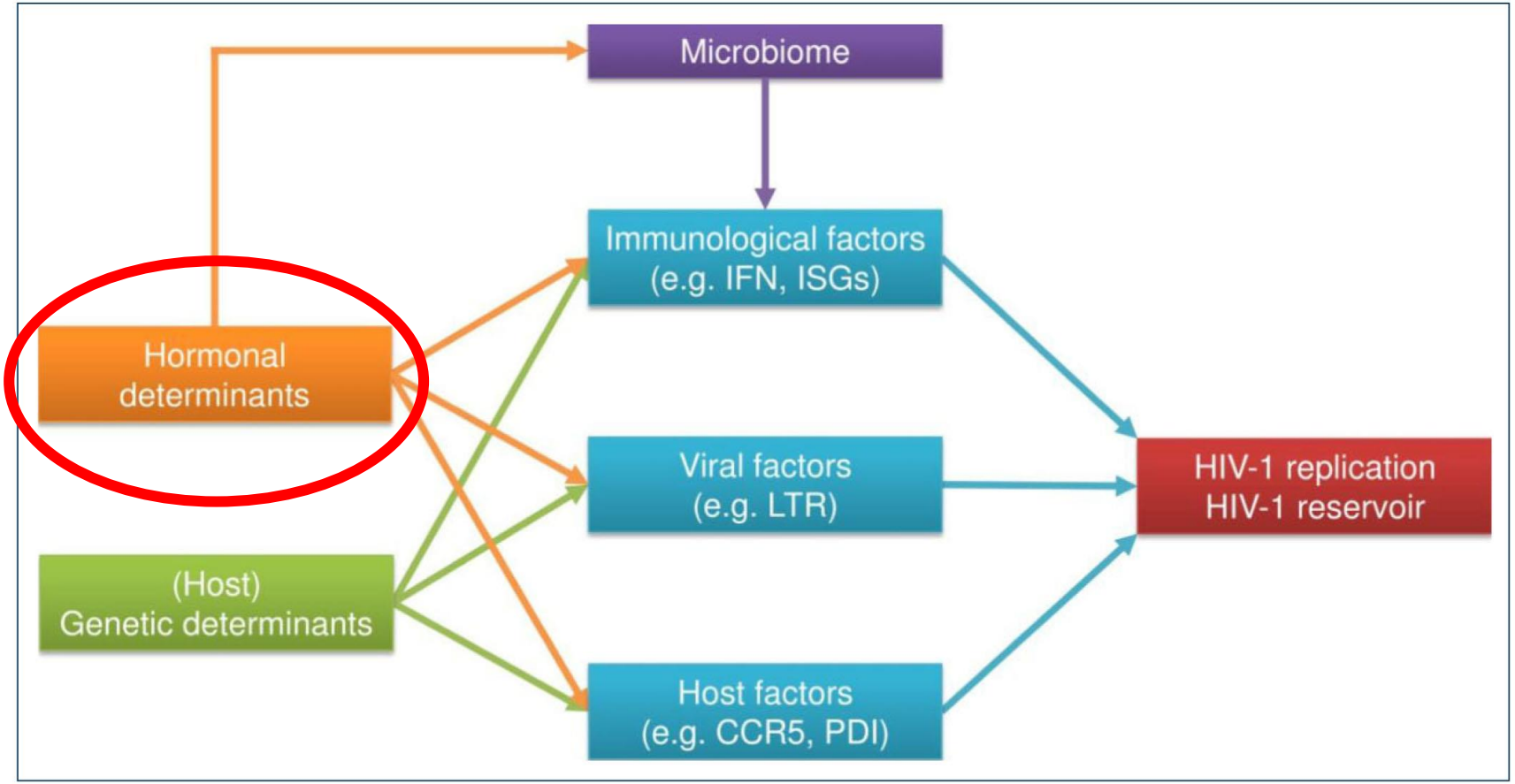

Figure 1. Summary of the multifactorial ramifications of sex-specific differences for HIV-1 infection. Immunological, viral and host factors regulate HIV-1 replication, as well as the creation and maintenance of the HIV-1 reservoir. These three factors are in turn regulated by genetic and hormonal determinants. The microbiome, furthermore, plays an important role in orchestrating sex differences of immune cells, as has been reviewed elsewhere [4,19,20]. IFN: interferon; ISG: interferon-stimulated genes; LTR: long terminal repeat; PDI: protein disulfide isomerase

the rate of disease progression is greater in women [6,7]. Additionally, sex hormone fluctuations in women have been associated with both protective and adverse effects. For example, relative to the follicular and luteal phases of the menstrual cycle, decreases in plasma viral load at ovulation, when estradiol levels are high, have been previously described [8], although others did not find any effect of the menstrual cycle on HIV-RNA levels in blood [9]. In contrast, analysis of genital secretions throughout the menstrual cycle demonstrated increased HIV-1 shedding during the luteal phase, when progesterone levels are higher, in some reports [9,10] while others did not find any pattern of genital tract

receptors (ER) present in the reproductive tract tissues and in immune cells in peripheral blood, including $CD4^+$ T-cells and macrophages, the two main HIV-target cells [16,17]. Binding of E_2 to its receptors results in modulation of the expression of multiple genes. Studies by others and us illustrate the broad spectrum of actions of E_2 on immune cells and the innate and adaptive immune response, including molecules and pathways involved in anti-viral innate immune responses [18,19,20]. With the exception of studies with isolated cells from the central nervous system or cell lines [21,22,23], very little is known about the direct

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Sex differences in adherence to highly active antiretroviral therapy: A meta-analysis

C. Ortego[a]*, T.B. Huedo-Medina[b], P. Santos[a], E. Rodríguez[a], L. Sevilla[a], M. Warren[b] and J. Llorca[c]

As the HIV epidemic has become feminized, it has also become more medicalized. HIV prevention and treatment strategies demand that PLWHA manage their disease through a regimen of highly active antiretroviral therapy (HAART). In order for HAART to be effective, patients need to maintain high levels of adherence to achieve viral suppression (Bangsberg et al., 2000; Paterson et al., 2000), prevent the development of resistant strains (Bangsberg et al., 2003; Harrigan et al., 2005; Sethi, Celentano, Gange, Moore, & Gallant, 2003), and reduce disease progression (Bangsberg et al., 2001) and death (Lima et al., 2009; Wood et al., 2003). The minimum cut-off for sufficient HAART adherence in order to achieve the highest treatment efficiency is not clearly established (Bangsberg, 2006; Turner, 2002), but usually ranges between ≥90% and ≥95%. (Bangsberg, 2006; Fogarty et al., 2002; Press, Tyndall, Wood, Hogg, & Montaner, 2002; Raffa et al., 2008).

Mantenere alti livelli di aderenza per ottenere:

- **Soppressione virologica**
- **Prevenire lo sviluppo di varianti resistenti**
- **Ridurre il rischio di progressione e morte**

Curr HIV/AIDS Rep (2011) 8:277–287
DOI 10.1007/s11904-011-0098-0

Women and Vulnerability to HAART Non-Adherence: A Literature Review of Treatment Adherence by Gender from 2000 to 2011

Cathy M. Puskas · Jamie I. Forrest · Surita Parashar · Kate A. Salters · Angela M. Cescon · Angela Kaida · Cari L. Miller · David R. Bangsberg · Robert S. Hogg

La popolazione femminile presenta una ridotta conoscenza della ART, un più alto tasso di interruzione e discontinuazione con conseguente viral rebound dopo soppressione rispetto alla popolazione maschile.

AIDS Care. 2014 ; 26(8): 959–967. doi:10.1080/09540121.2013.873765.

Gender moderates the influence of psychosocial factors and drug use on HAART adherence in the context of HIV and childhood sexual abuse

Sarah M. Wilson, MA[a,b], Kathleen J. Sikkema, PhD[a,b], and Krista W. Ranby, PhD[c]

Ridotta aderenza della popolazione femminile è associata a:

- ✓ **Depressione**
- ✓ **Mancanza di relazioni interpersonali di supporto**
- ✓ **Giovane età**
- ✓ **Abuso di droghe ed alcool**
- ✓ **Etnia nera**
- ✓ **Assenza di stato gravidico**
- ✓ **Terapia costituita da 6 o più compresse al giorno**
- ✓ **Alto numero di figli**
- ✓ **Percezione di sovrappeso**
- ✓ **Disturbi del sonno**
- ✓ **Incremento dei livelli di stress**
- ✓ **Stato socio-economico precario**

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Più alta percentuale di aderenza nella popolazione femminile:

- ✓ **Studio condotto in lingua inglese**
- ✓ **Studio condotto in paese industrializzato**
- ✓ **Quando la casistica presentava una più bassa conta al basale di CD4+**
- ✓ **Quando la casistica presentava una più alta numerosità di donne vedove**

GRACE: DRV/RTV + Optimized Background Regimen in Tx-Exp'd Pts

Wk 48 Outcome, %	Women	Men	*P* value
Virological response			
▪ By ITT analysis	50.9	58.5	.067
▪ Excluding pts who withdrew*	73.0	73.5	.44
Discontinuations	32.8	23.2	.042

*For reasons other than virological failure.

Currier J, et al. Ann Intern Med. 2010;153:349-357.

Biomedicine & Pharmacotherapy 68 (2014) 385–390

Available online at ScienceDirect www.sciencedirect.com

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Original article

Gender differences in HIV infection: Is there a problem? Analysi the SCOLTA cohorts

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i[b], C. Martinelli[e],
j], C. Grosso[k], A. Di

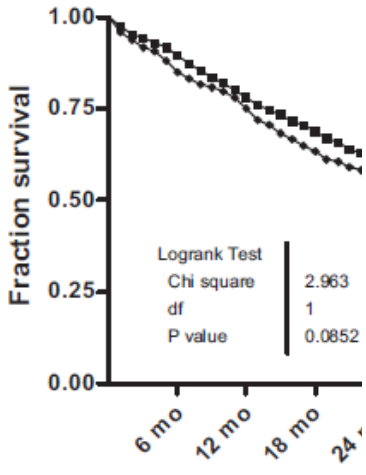
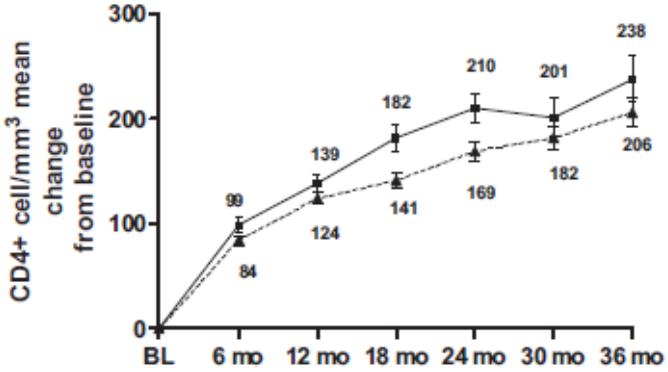
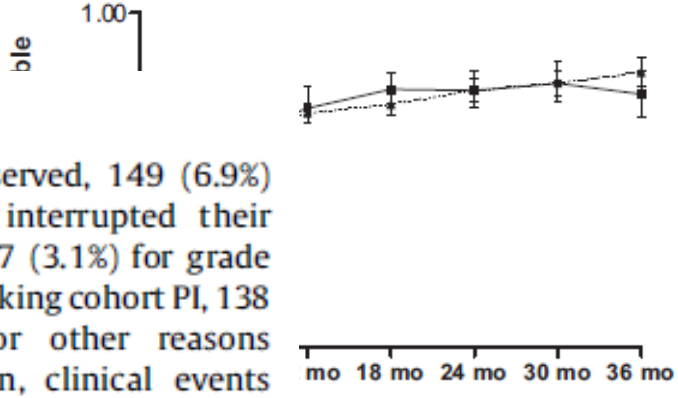


Fig. 2. Kaplan-Meyer curve for PI-based an
by gender, in 607 women and 1547 men, f

1a)





CD4+ cell count changes over time, and b: bjects with undetectable HIV RNA, by I-based antiretroviral treatment, from the

4.4. Reason for discontinuation

Overall, 51 (2.4%) patients died while observed, 149 (6.9%) experienced a virologic failure, 164 (7.6%) interrupted their treatment for grade 1-2 adverse events and 67 (3.1%) for grade 3-4 adverse events, 146 (6.8%) wanted to stop taking cohort PI, 138 (6.4%) had a simplification, 122 (5.7%) for other reasons (adherence, structured treatment interruption, clinical events and others), 330 (15.3%) were lost at follow-up and 987 (45.8%) were still on treatment when the study ended. These proportions were remarkably different only as regards discontinuation due to the patient's will (10.7% in women and 5.2% in men, heterogeneity chi square = 0.002).

In the whole sample, we did not find any other significant difference regarding reason for discontinuation of PI-based treatments. However, performing the analysis by drug, we found that in the atazanavir cohort women were more likely to discontinue or switch treatment for grade 1-2 adverse events (6.8% *vs.* 3.0%), low adherence (3.4% *vs.* 1.2%) and patient's will (7.7% *vs.* 3.9%) (heterogeneity chi-square $P = 0.048$).

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Women Facing HIV. Key Question on Women with HIV Infection: Italian Consensus Workshop

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Statement 1.5 Gender Differences in Pharmacokinetics

Despite the fact that there is no weight-guided dosage of ARV drugs, gender differences in bio-availability, distribution, metabolism and elimination of antiretroviral drugs have been demonstrated [24–31]. Due to possible interferences of hepatic metabolism, physicians should ask about the usage of oral
both ARV and contrac
drug monitoring (TDM
adverse events or a low
to be related with the lo

Più alto tasso di eventi avversi… i sintomi gastroenterici sono più frequenti nelle donne, così come le alterazioni metaboliche (glucosio e lipidi), la diversa distribuzione del grasso corporeo (lipodistrofia).

Evaluation of sexual dysfunction in women living with HIV

EACS guideline:

When sexual complaints exist:	What is the exact nature of the problem? In which phase(s) of the sexual response cycle does the problem occur?	1. **Desire** (lack of sexual desire or libido; desire discrepancy with partner; aversion to sexual activity) 2. **Arousal** (difficulties with physical and/or subjective sexual arousal; difficulties or inability to achieve or sustain an erection of sufficient rigidity for sexual intercourse MEN; i.e. erectile dysfunction; lack or impaired nocturnal erections MEN; difficulties lubricating WOMEN; difficulties sustaining arousal) 3. **Orgasm** (difficulties experiencing orgasm) 4. **Pain** (pain with sexual activity; difficulties with vaginal/anal penetration–anxiety, muscle tension; lack of sexual satisfaction and pleasure)

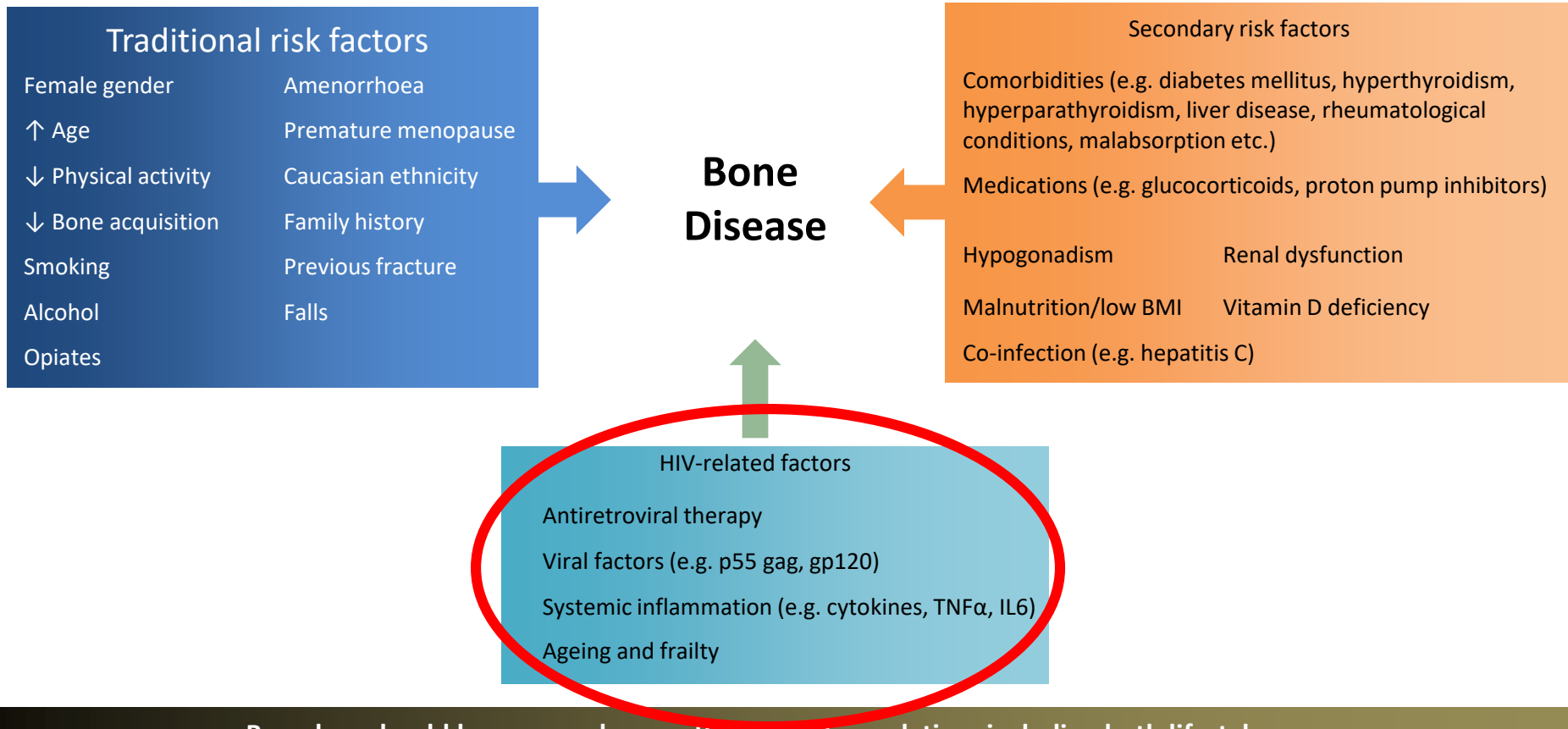
Female Sexual Function Index (FSFI) ©

HIV Drug Interactions

UNIVERSITY OF LIVERPOOL

	Abacavir	Bictegravir/FTC/TAF	Darunavir/cobicistat/FTC/TAF	Dolutegravir/rilpivirine	Elvitegravir/cobicistat/FTC/TAF	Elvitegravir/cobicistat/FTC/TDF	Emtricitabine/TAF	Rilpivirine/FTC/TAF
Drospirenone (HRT)	◆	◆	■	◆	■	■	◆	◆
Dydrogesterone (HRT)	◆	◆	■	◆	■	■	◆	◆
Levonorgestrel (HRT)	◆	◆	■	◆	■	■	◆	◆
Norethisterone [Norethindrone] (HRT)	◆	◆	■	◆	■	■	◆	◆
Norgestrel (HRT)	◆	◆	■	◆	■	■	◆	◆

Multifactorial risk of bone disease in postmenopausal women living with HIV[1,2]

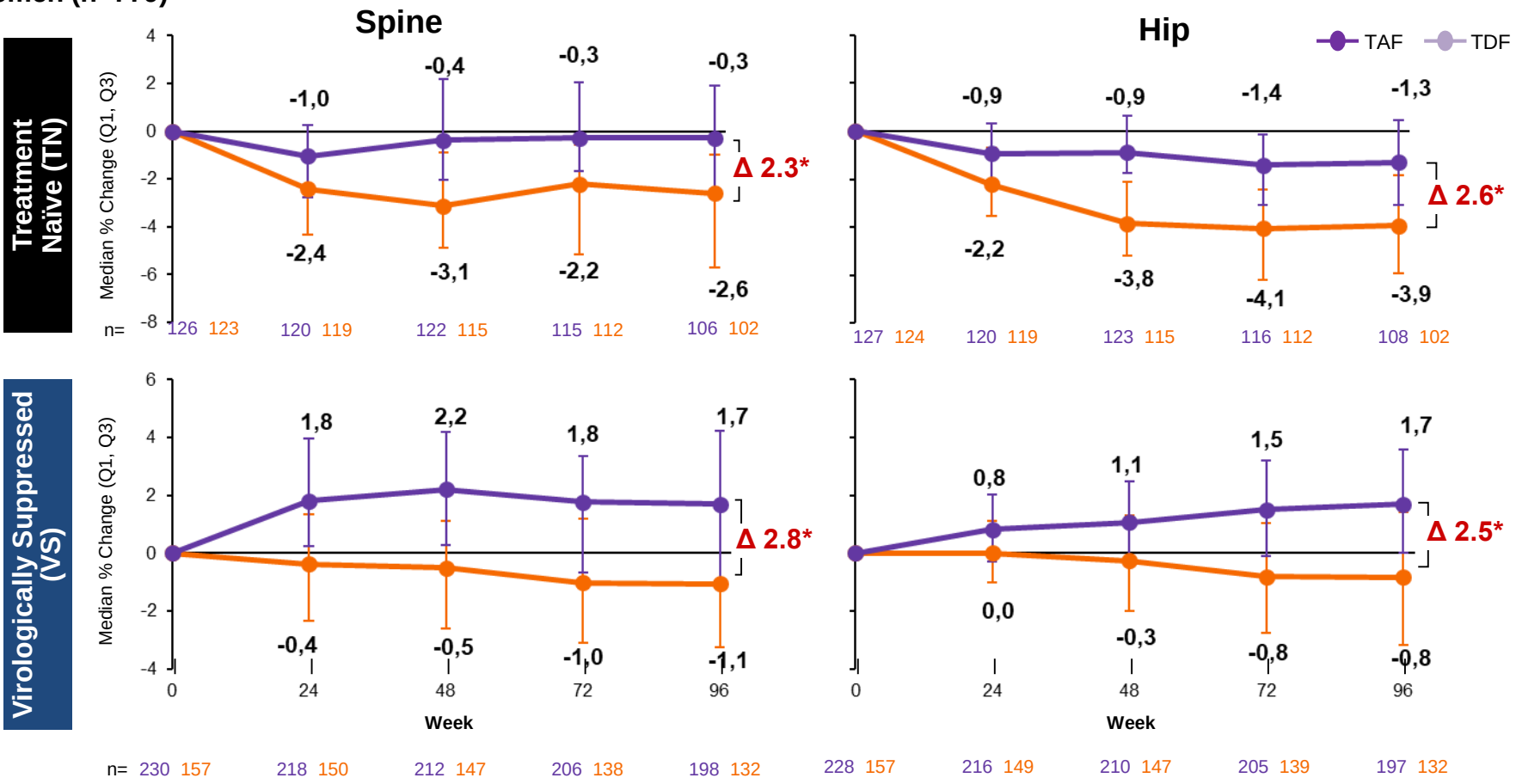


Bone loss should be managed as per the general population, including both lifestyle modifications and pharmacologic therapy where appropriate[3]

- BMI, body mass index
- 1. Bull L et al. *Post Reprod Health* 2018;24(1):19-25; 2. Finnerty F et al. *Maturitas* 2017;95:50–54; 3. Andany N et al. *Int J Womens Health* 2016;8:1–22.

Women switching from TDF to TAF had improvements in BMD over 96 weeks

BMD change through Week 96 in a pooled analysis of 7 clinical trials comparing TAF- and TDF-based regimen in women (n=779)



Women initiating TAF had less BMD decline vs. TDF, and women switching to TAF from TDF had improvements in BMD.

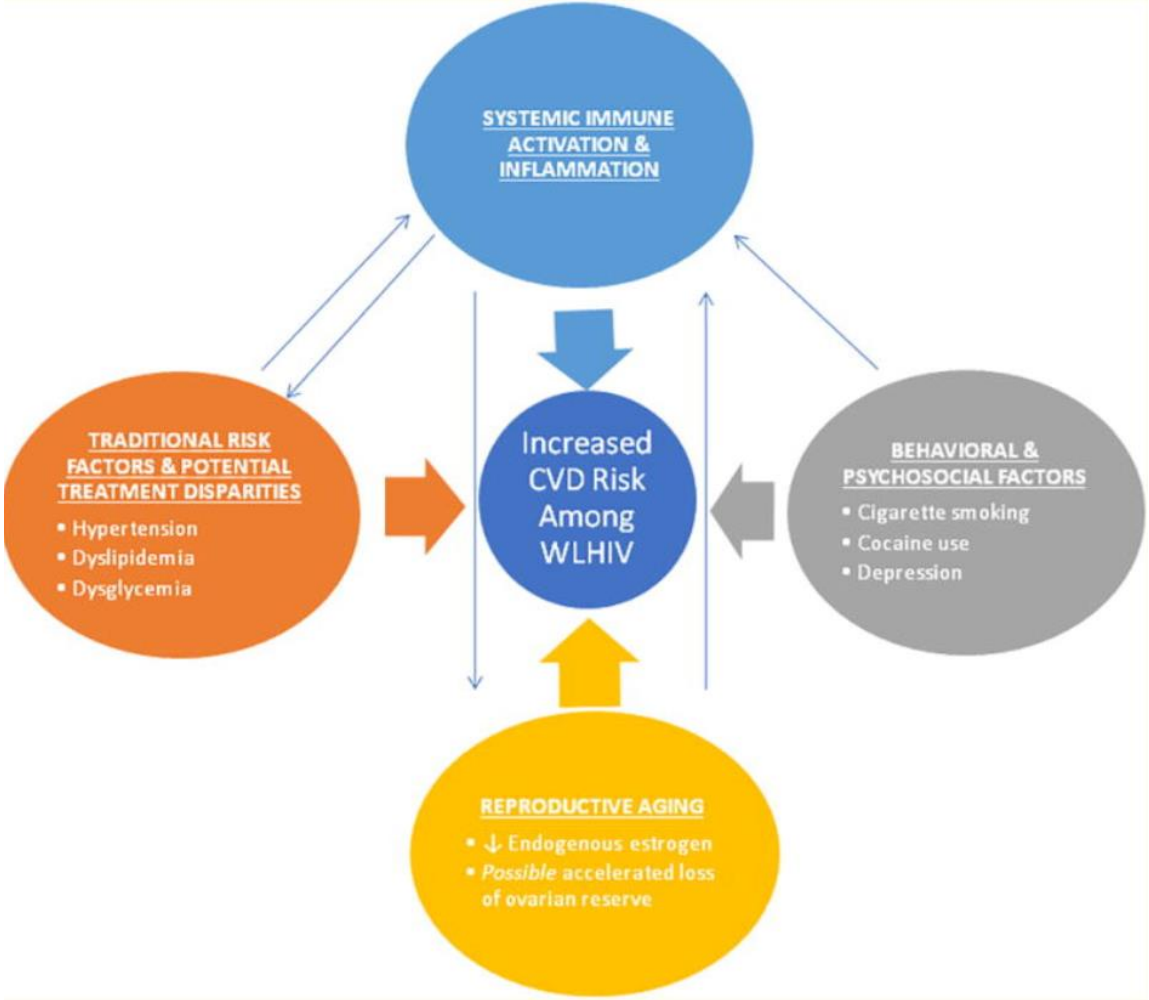
* p<0.001. P-values were from the ANOVA model including study and treatment as fixed effects.

Abbreviations to be defined

Thompson M, et al. CROI 2019. Seattle, WA. Poster 519

Multiple factors increase CVD risk for postmenopausal women living with HIV

- WLHIV face a 2 to 4-fold increased risk for MI, stroke, and heart failure compared with HIV uninfected women[1]
- Women have increased incidence of HTN, diabetes, and dyslipidemia after menopause[1]
- In D:A:D, WLHIV were less likely to receive therapeutic interventions for established cardiometabolic risk factors[2]



HTN, hypertension MI, myocardial infarction; WLHIV, women living with HIV

Stone L, et al. Curr Opin HIV AIDS. 2017 Nov; 12(6): 585–593. 2. Hatleberg CI, et al. J Int AIDS Soc. 2014;17(4 Suppl 3):19516

OUTLINE

- Linee guida
- Perché:
    - Comorbidità
    - Weight gain
    - Gravidanza e PK/safety
- Clinical trials: a never ending story

Nell et al. BMC Infectious Diseases (2015) 15:85
DOI 10.1186/s12879-015-0836-9

Distinct gender differences in anthropometric profiles of a peri-urban South African HIV population: a cross sectional study

Theodore A Nell[1,2*], Maritza J Kruger[1*], Dillan C Beukes[1], Esme Calitz[3], Rehana Essop[4] and M Faadiel Essop[1]

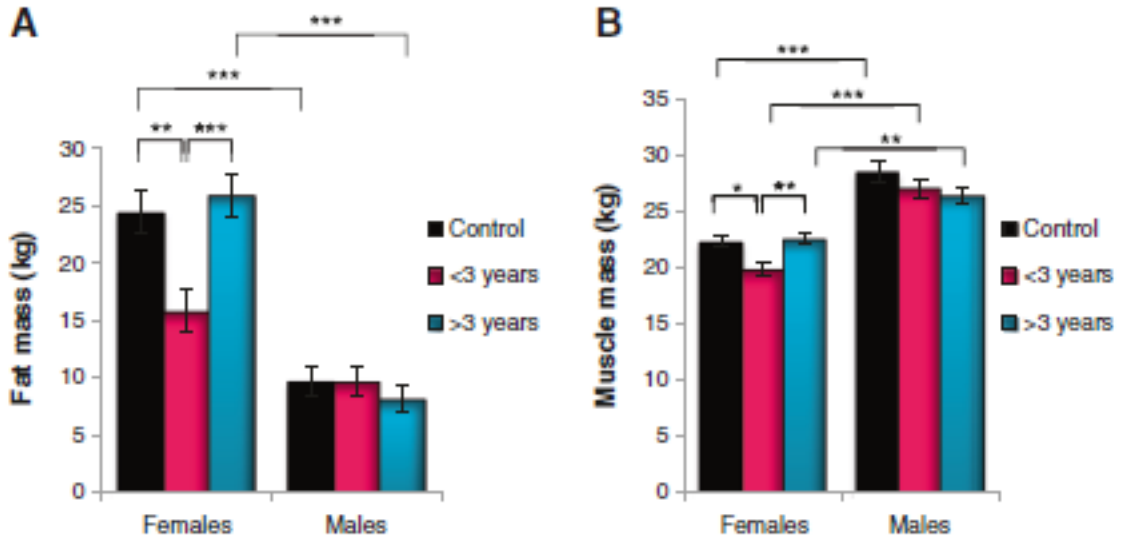
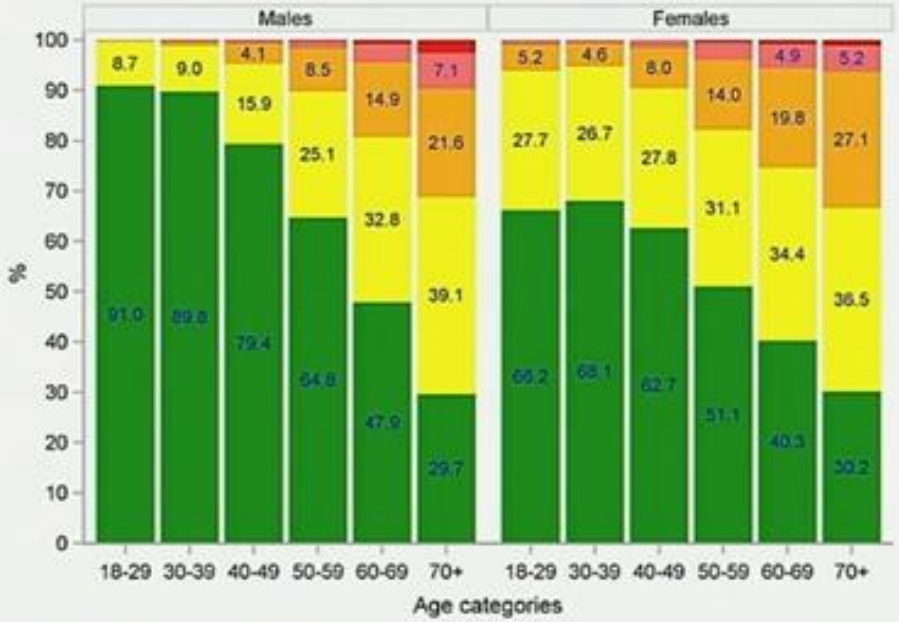
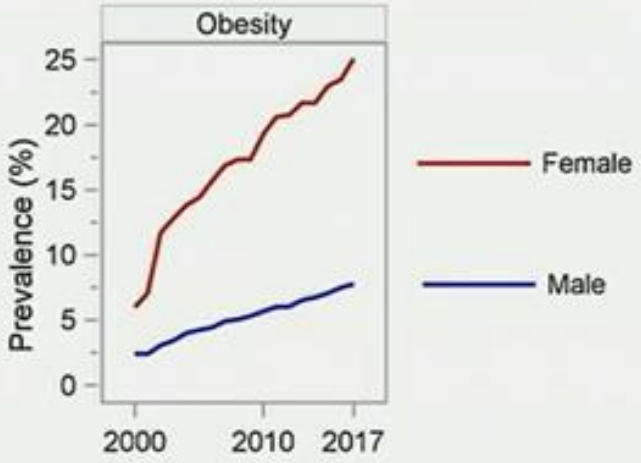


Figure 3 Fat mass (A) and Muscle mass (B) according to gender and treatment (*p < 0.05; **p < 0.01; ***p < 0.001).

Multimorbidity and crude mortality rates

Multimorbidity by age and gender in 2017





HIV Monitoring

Risk Factors for Excess Weight Gain Following Switch to Integrase Inhibitor–based ART

J. E. Lake et al.

Greater Weight Gain Among Treatment-naive Persons Starting Integrase Inhibitors

K. Bourgi et al.

Weight Gain During Treatment Among 3,468 Treatment-experienced Adults with HIV

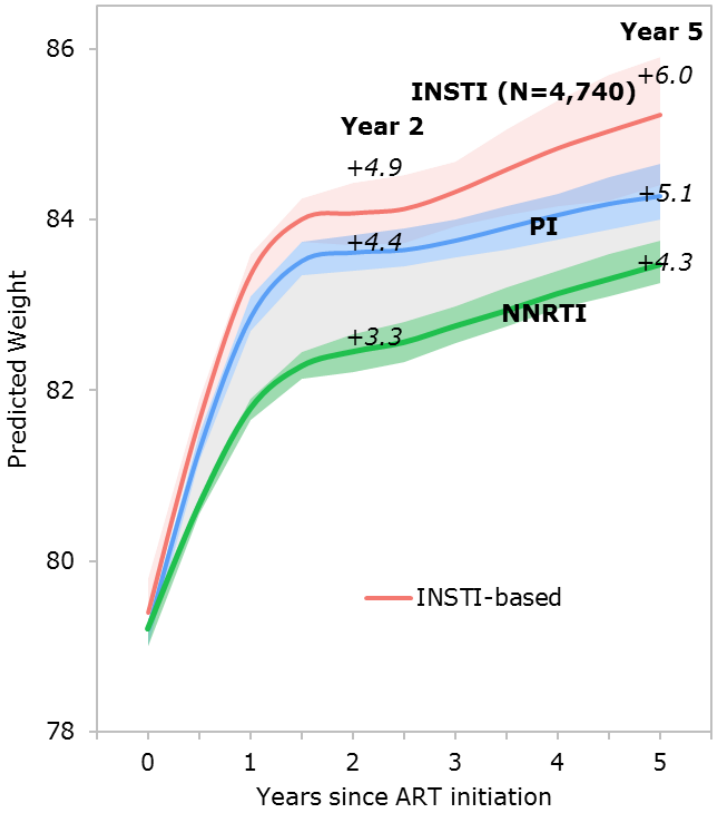
G. A. McComsey et al.

CROI 2019, Seattle, USA, Poster and Themed Discussion 669, 670, 671

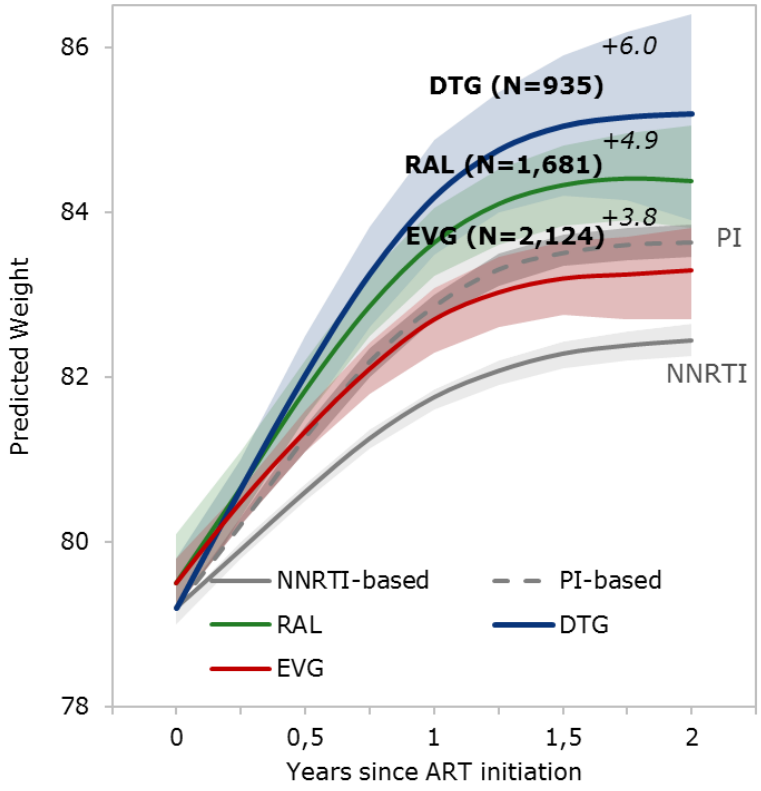
NA ACCORD: INSTI-Regimens in ART Naïve Results

- Weight gain associated with INSTI-based regimens did not vary by male vs. female or white vs. non-white
- Treatment-naïve PLWH starting INSTI, especially DTG and RAL, were at higher risk of weight gain compared to NNRTI-class regimens
- Weight gain among patients starting INSTI was not uniform: with PLWH starting RAL and DTG gaining significantly more weight than PLWH starting EVG

Predicted weight changes within 5 years of ART initiation by ART class

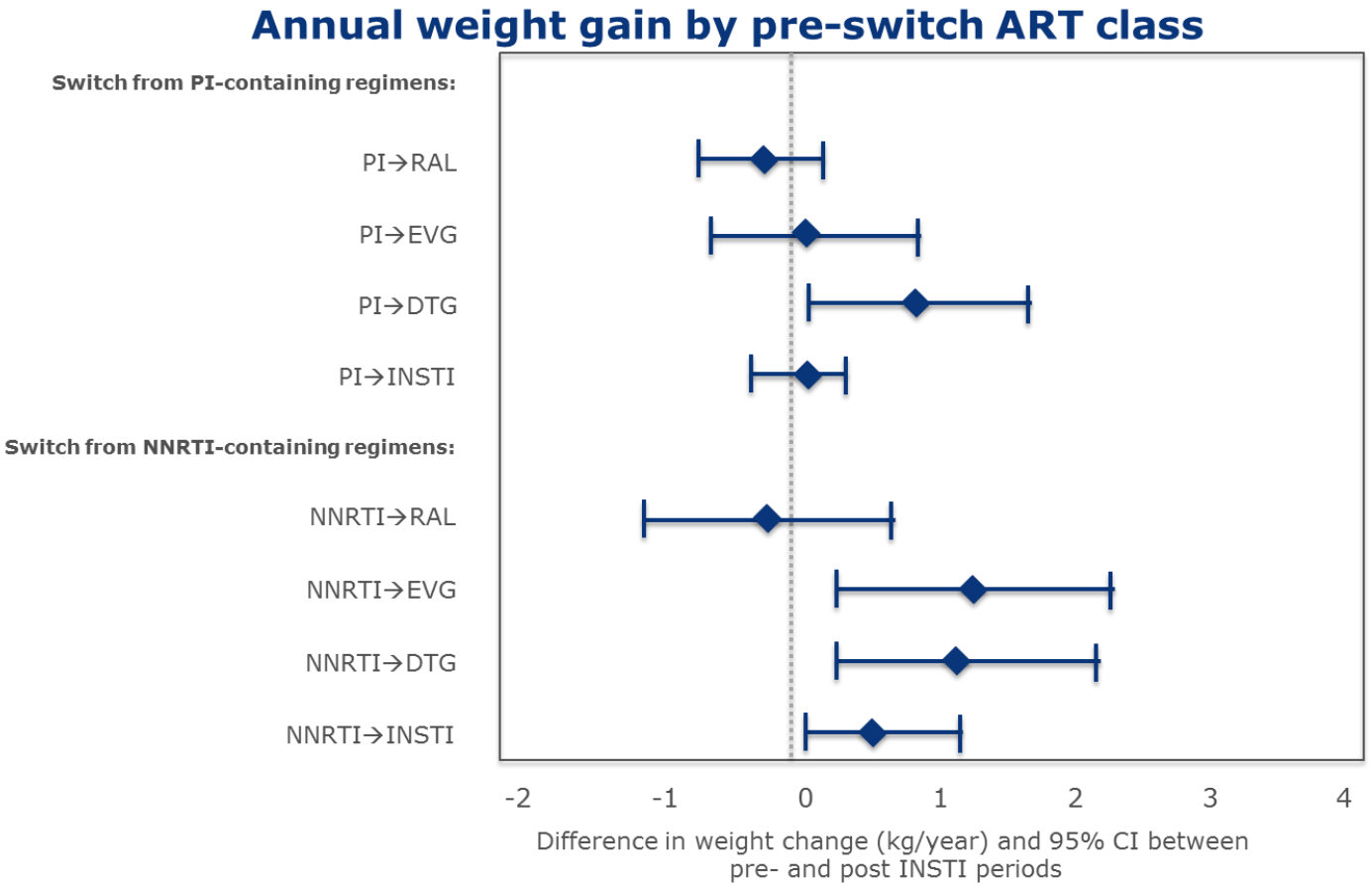


Predicted weight changes within 2 years of ART initiation by INSTI and ART class



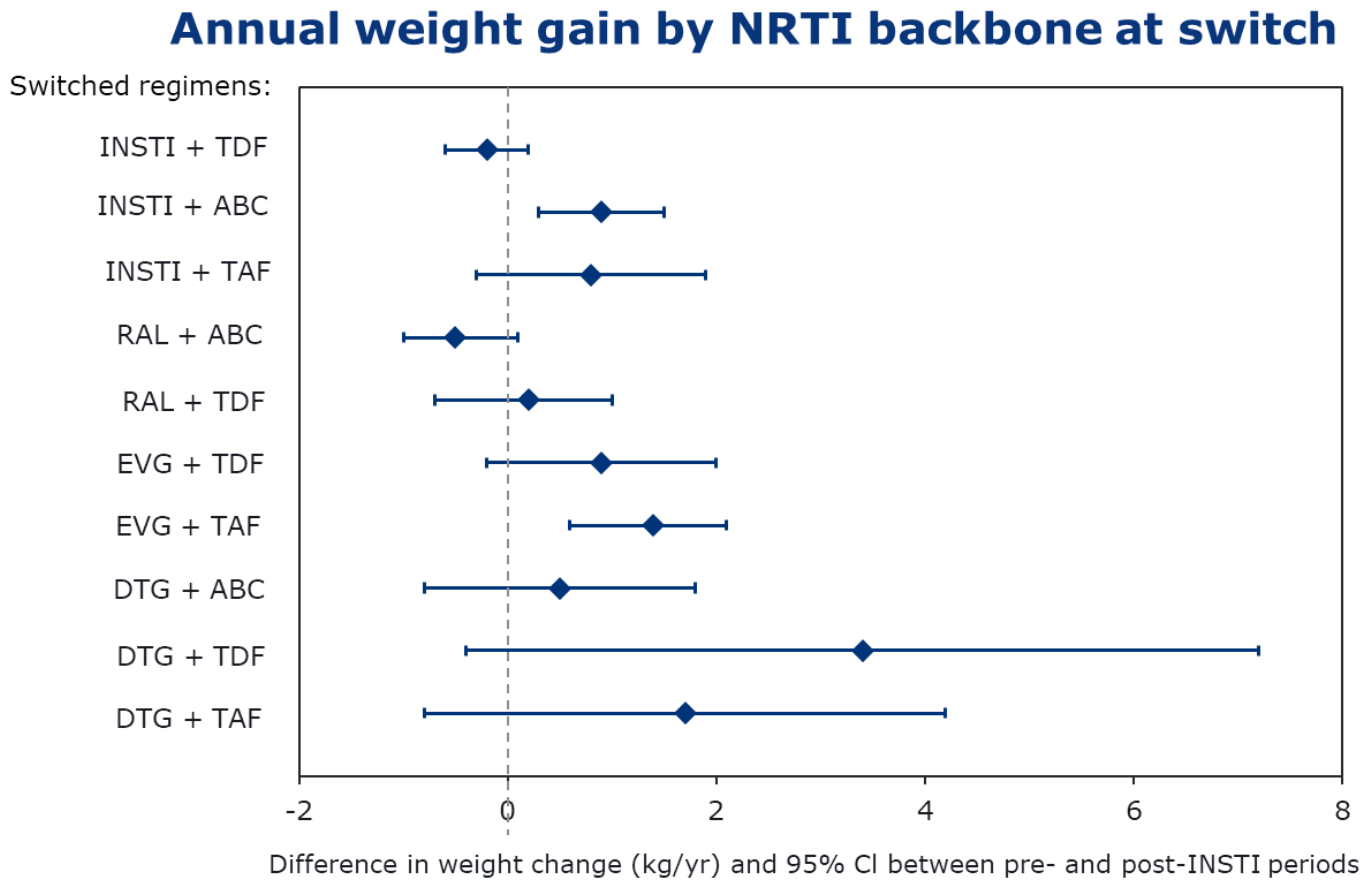
ACTG: Weight Gain on INSTI-Based Regimens Results by Pre-Switch ART Class

- Statistically **significant weight gain following a switch to DTG from PI or NNRTI, and switch to EVG from NNRTI** (p<0.05, limited sample size)



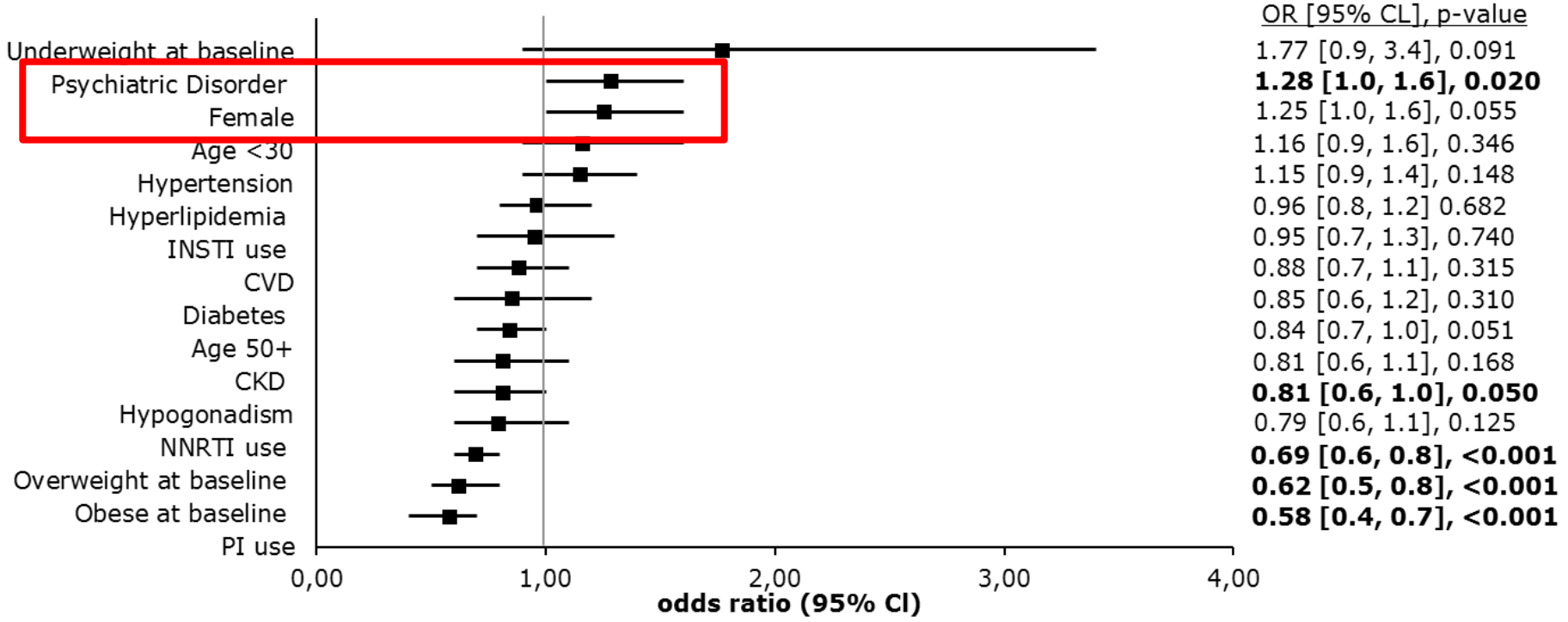
ACTG: Weight Gain on INSTI-Based Regimens Results by NRTI-Backbone

- Statistically **significant weight gain following a switch to any INSTI with ABC and switch to EVG with TAF** ($p<0.05$, limited sample size)
- 61% of ABC, 87% of TDF and 4% of TAF use at switch to INSTI received the same NRTI backbone pre-switch



WEIGHT GAIN IN ART-EXPERIENCED ADULTS IN USA: MULTIVARIATE ANALYSIS OF WEIGHT GAIN ≥3%

- Negatively associated with weight gain ≥3% (logistic regression):
  - Overweight or obese at BL, hypogonadism, use of PI-based therapies
- Positively associated with weight gain (logistic regression):
  - Psychiatric disorders
- Not significantly associated with weight gain ≥3% (logistic regression):
  - INSTI-based ART



OUTLINE

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    - Weight gain
    - Gravidanza e PK/safety
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What are potential considerations for women with HIV?

- Placental abruption
- Placenta praevia
- Malpresentation
- Low birthweight
- Macrosomia
- Preterm delivery
- Post term delivery
- Post partum haemorrhage

- Assisted conception
- Multiple pregnancies

- Pre-eclampsia
- Gestational diabetes

- Pre-existing medical conditions
- Hypertension
- Obesity
- Diabetes

- Impaired myometrial function
- Emergency caesarean section & instrumental deliveries

- Stillbirth
- Neonatal mortality

- Maternal mortality

- Congenital malformations

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* DTG **after 1st trimester**†	RAL
NRTI	ABC§/3TC or TDF/FTC or TDF/3TC	ABC*/3TC (or FTC) or TDF/FTC (or 3TC)
PI	ATV/r DRV/r	ATV/r 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

….guardando al futuro?

Backbone….TAF?

Booster….COBI?

INSTI….BIC?

INSTI….DTG?

….guardando al futuro?

Backbone….TAF?

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INSTI….BIC?

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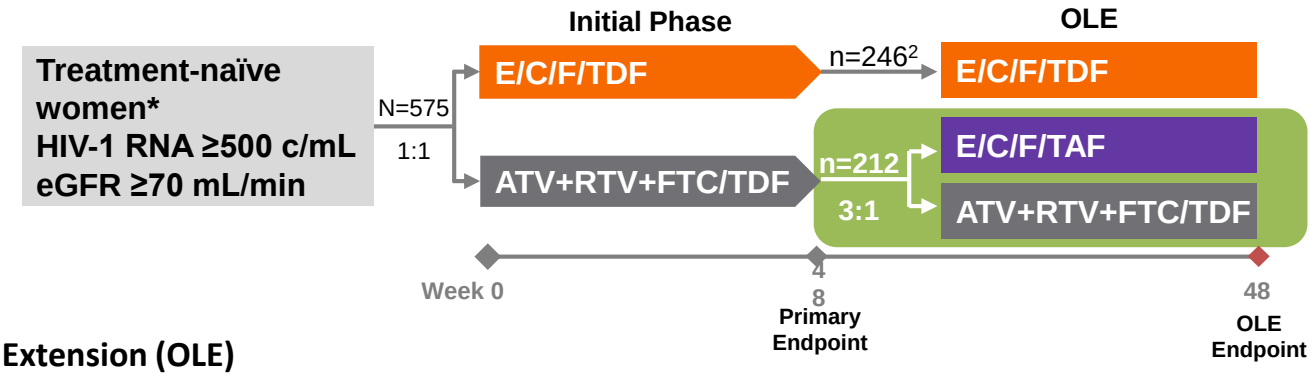
Study Design

Phase 3b, randomized, double-blind, active-controlled phase with re-randomized, open-label, active-controlled, extension phase



Open Label Extension (OLE)

- Inclusion criteria: VL < 50 c/mL & GFR ≥ 50 mL/min
- W48 rollover from ATV+RTV+FTC/TDF to E/C/F/TAF vs continuing PI regimen

Initial Phase Primary Endpoint (HIV-RNA < 50 c/mL based on W48 FDA snapshot analysis)

- E/C/F/TDF (87%) was superior to ATV+RTV+TVD (81%) at Week 48

* Women of childbearing potential had to agree to utilize protocol-recommended contraception methods, be nonheterosexually active, or practice sexual abstinence. eGFR, estimated glomerular filtration rate.

1. Hodder S, et al. CROI 2017. Seattle, WA. Poster #443; 2. Squires K, et al. International Workshop HIV & Women 2017; Seattle, WA. Oral #10

Pregnancies through Week 48

- Per study protocol, subjects who became pregnant had choice of staying on study drug.

	E/C/F/TAF n=159	ATV+RTV+FTC/TDF n=53
Pregnancies, n	14	6
Live birth	3	3
Elective termination	4	1
Miscarriage	5	1
Outcome not reported	2	1

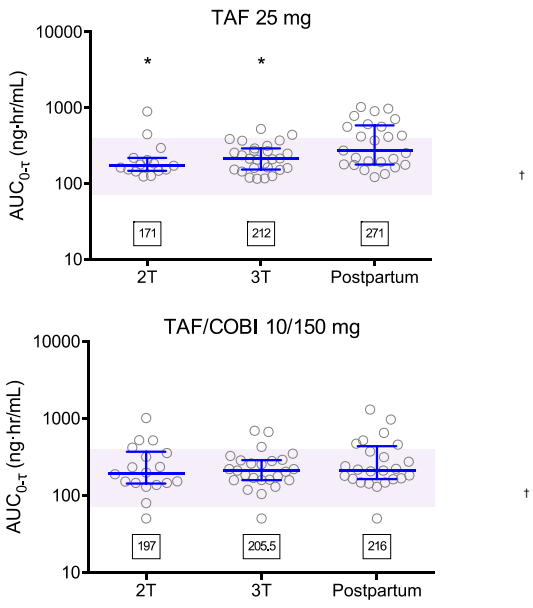
- Of the E/C/F/TAF pregnancies above:
  - Only one subject discontinued E/C/F/TAF after pregnancy confirmation. All other subjects chose to continue study drug.

Hodder S, et al. CROI 2017. Seattle, WA. Poster #443
Data on File. Gilead Sciences.

TAF PK with and without COBI in Pregnancy

IMPAACT P1026s

Ongoing non-randomized, multicenter Phase 4 prospective PK and safety study in HIV-infected pregnant women (n=58) receiving R/F/TAF or E/C/F/TAF



† Grey shading represents 5th to 95th percentile AUC for TAF (given as GEN) in the general population

Momper JD, et al. AIDS 2018. Amsterdam, NL. THAB0302

Safety Results

- Maternal safety: One grade 2 AE (probable hepatic steatosis) considered possibly related
- HIV status of infants: 46 (79%) uninfected; 8 (14%) indeterminate; 4 (7%) pending
- TAF below limit of quantitation in all 15 cord blood samples
- 2 birth abnormalities possibly related to ART:
  - Left congenital pseudoarthrosis clavicle (TAF started at 25 5/7 weeks)
  - Renal cyst (TAF started prior to conception)

Conclusions

- **Plasma TAF exposure during pregnancy and postpartum were comparable with non-pregnant adults**
- TAF was safe and well-tolerated in mothers and infants
- **No transplacental passage of TAF observed to date**
- Additional safety and outcome data are needed in pregnant women

….guardando al futuro?

Backbone….TAF?

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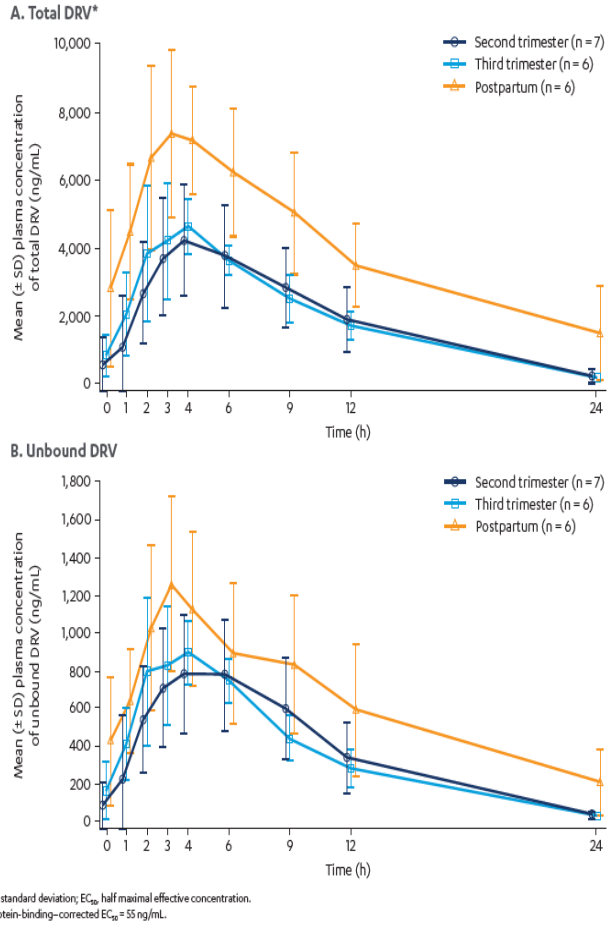
INSTI….BIC?

INSTI….DTG?

DRV/c PK in pregnancy

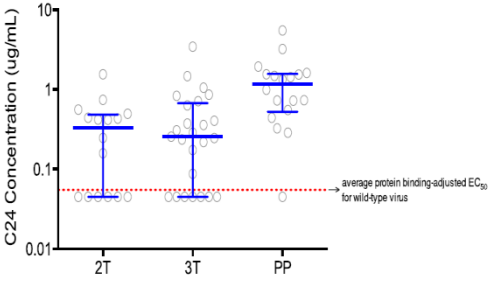
- Janssen PK study of DRV/c in pregnancy[1]
  - The pharmacokinetic data from the Phase 3b study TMC114HIV3015 in 6 pregnant women demonstrated that the AUC of DRV/c was 56% and 50% lower during the 2nd and 3rd trimesters of pregnancy, respectively, compared with 6 to 12 weeks postpartum
  - Mean DRV C_{min} concentrations were around 90% lower during the 2nd and 3rd trimesters of pregnancy as compared to postpartum
  - No evidence of MTCT was observed and 5 of 6 women were virologically suppressed at study completion

- IMPAACT PK study of DRV/c during pregnancy and postpartum[2]
  - **In women taking DRV/c the exposure to DRV appeared to be lower in pregnancy compared to postpartum**
  - Additional PK, safety, and outcome data in pregnant women are needed before DRV/COBI can be recommended for use during pregnancy



SD, standard deviation; EC_{50}, half maximal effective concentration.
*Protein-binding–corrected EC_{50} = 55 ng/mL.

Figure 2. Darunavir C_{24} Ante- and Postpartum

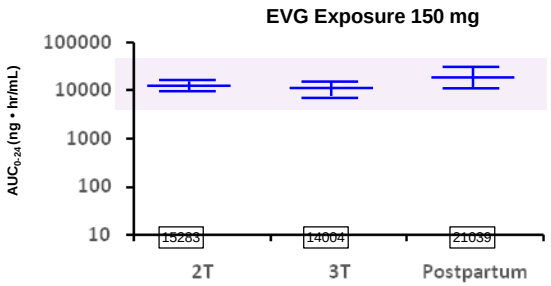


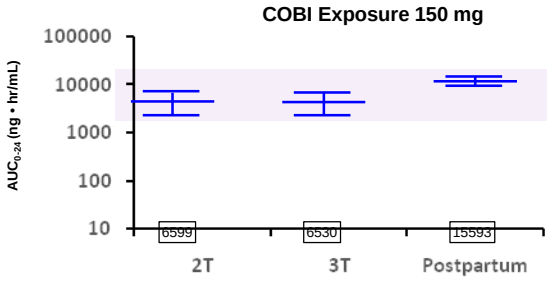
Concentrations below the limit of quantitation (BLOQ; 0.9 µg/mL) are displayed as ½ the lower limit of quantitation (1.95 ng/mL).

EVG and COBI PK in Pregnancy

IMPAACT P1026s:

PK and safety in HIV-infected pregnant women (n=30) receiving EVG and COBI as part of EVG 150mg/COBI 150mg





Median AUC_{0-24} and interquartile ranges shown above for EVG and COBI.
GMR = Geometric mean ratio

Momper JD, et al. AIDS 2018. 32:3205-2516

Neonatal Safety

- No neonatal plasma samples had measurable EVG concentration (> 10 ng/mL) at the final washout sample between 5-9 days of life.
- Cobicistat was not detected in any neonatal plasma sample after birth.

Limitations

- Postpartum AUC_{0-24} used to calculate GMR's for COBI were almost twice as high as in nonpregnant subjects.
- Administration with food, which is a requirement for EVG/c, was not standardized in study.

Conclusions

- **EVG and COBI exposures at 2nd and 3rd trimesters were lower compared to postpartum which may increase risk of virologic failure and vertical transmission**

….guardando al futuro?

Backbone….TAF?

Booster….COBI?

INSTI….BIC?

INSTI….DTG?

EVG and BIC Use During Pregnancy and Risk of Neural Tube Defects (NTD)

- Pregnancy exposures and outcomes reported retrospectively or prospectively
  - Clinical trials
  - Literature
  - Antiretroviral Pregnancy Registry (APR)
  - Postmarketing spontaneous and solicited cases
- Exposures and cases
  - All pregnancy exposures and all cases reporting events in the system organ class of congenital, familial, and genetic disorders
  - All cases of NTDs regardless of the trimester of exposure or if unknown timing

Elvitegravir

- 630 pregnancies; 155 prospective at preconception or 1st trimester
  - No prospective NTD cases
  - Two retrospective cases of NTDs with exposure prior to (1) or near conception (1)*
  - Cannot be distinguished from the background rate

Bictegravir

- 25 pregnancies; 18 prospective at preconception or 1st trimester
  - No cases of NTDs among a small number of exposed pregnancies

- **Currently, no evidence of an increased risk of NTDs with the use of EVG or BIC.**
- **NTD monitoring via Gilead's pharmacovigilance process and APR are ongoing.**
- **E/C/F/TDF , E/C/F/TAF , B/F/TAF should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus[1].**
- A prevalence rate could not be derived from these data as many cases originated from retrospective reports and were drawn from a population in which the number of exposed pregnancies is unknown. 1-Genvoya, Stribild, Biktarvy SmPC section 4.6)

Farrow T, et al. HIV Drug Therapy. 2018. Glasgow, UK. Poster 30

….guardando al futuro?

Backbone….TAF?

Booster….COBI?

INSTI….BIC?

INSTI….DTG?

Interim Guidance about the Use of Dolutegravir in Pregnancy

DHHS December 7, 2018 update:

- **DTG is not recommended** for use in pregnant women **during the first trimester*** and in **nonpregnant women who are trying to conceive**, due to concerns about a possible increased risk of neural tube defects (NTDs) (AIII).
- For pregnant women who are receiving DTG and who present to care during the first trimester provide counseling about the risks and benefits of continuing DTG or switching to another ARV regimen (AIII). The following considerations should be addressed:
  - NTDs may have already occurred;
  - Depending on the current gestational age, the additional risk of NTDs developing during the remaining time in first trimester may be small;
  - There is a **background risk of NTDs regardless of antiretroviral treatment (ART) regimen or HIV status** (this risk ranges from 0.05% to 0.1% for women without HIV, and women with HIV who are receiving ART that does not include dolutegravir); and
  - Changes in ART, even in the first trimester, are often associated with viral rebound that may increase the risk of perinatal HIV transmission.
- When DTG use is continued after delivery, clinicians should recommend the use of postpartum contraception and discuss contraceptive options with patients (AIII).

* 1st trimester = less than 14 weeks [up to 13 6/7 weeks] gestational age by last menstrual period.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion*

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.Available at: http://aidsinfo.nih.gov/guidelines

Lo studio, che ha esaminato bambini nati da 11.558 donne affette da HIV in Botswana, ha mostrato che lo 0,9% dei bambini (4 su 426) le cui madri sono rimaste incinta mentre assumevano dolutegravir avevano un difetto del tubo neurale, rispetto allo 0,1% dei bambini (14 di 11.173) le cui madri hanno preso altri medicinali per il trattamento dell'HIV.

OUTLINE

- Linee guida
- Perché:
  - Comorbidità
  - Weight gain
  - Gravidanza e PK/safety
- Clinical trials: a never ending story

  TAF ABC/3TC/DTG D/C/F/T 2DR

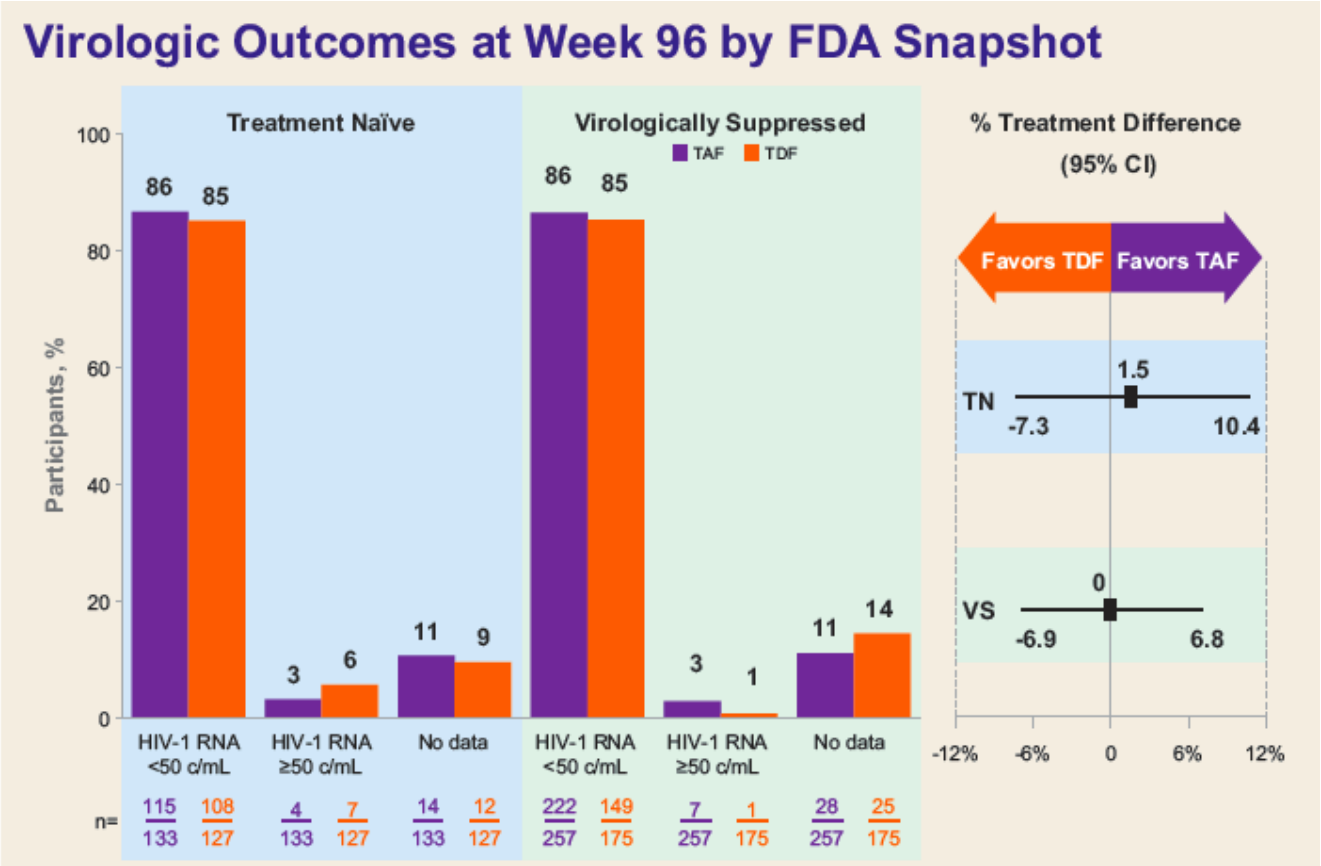
OUTLINE

- Linee guida
- Perché:
  - Comorbidità
  - Weight gain
  - Gravidanza e PK/safety
- Clinical trials: a never ending story
  - TAF ABC/3TC/DTG D/C/F/T 2DR

Virologic outcomes with TAF-based regimen were non-inferior to TDF-based regimen in women

Pooled analysis of 7 clinical trials comparing TAF- and TDF-based regimen in women (n=779)

Study (n=)	Treatment comparison
Treatment naive (2 studies, 260 women)	
292-0104/0111 (N=867+866)	E/C/F/TAF vs E/C/F/TDF
Virologically suppressed (5 studies, 519 women)	
380-1878 OL (N=577)	B/F/TAF vs bPI-regimens
366-1160 (N=875)	FTC/RPV/TAF vs EFV/FTC/TDF
366-1216 (N=630)	FTC/RPV/TAF vs FTC/RPV/TDF
311-1089 (N=663)	F/TAF + 3rd agent vs F/TDF + 3rd agent
292-0109 OL (N=1436)	E/C/F/TAF vs TDF-containing regimens



Thompson M, et al. CROI 2019. Seattle, WA. Poster 519

Study Design

Phase 3, multicenter, randomised, open-label, active-controlled study

HIV Suppressed Women on E/C/F/TAF or E/C/F/TDF or ATV+RTV+F/TDF
HIV-1 RNA <50 c/mL for ≥6 mos
$eGFR_{CG}$ ≥50 mL/min

1:1

n=234 → **Switch to B/F/TAF QD***

n=236 → **Stay on baseline regimen (SBR)†**

Day 1 → Week 48 **Primary Endpoint**

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

ClinicalTrials.gov Identifier: NCT02652624

Primary Endpoint

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

Secondary Endpoint

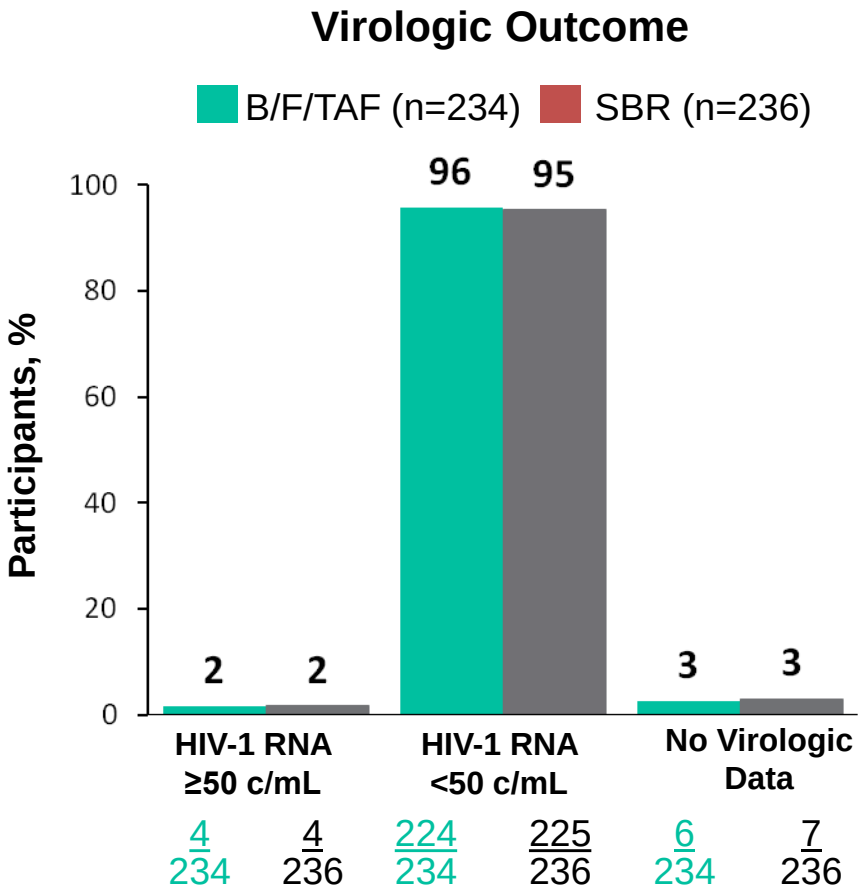
- HIV-1 RNA <50 copies/mL at Week 48

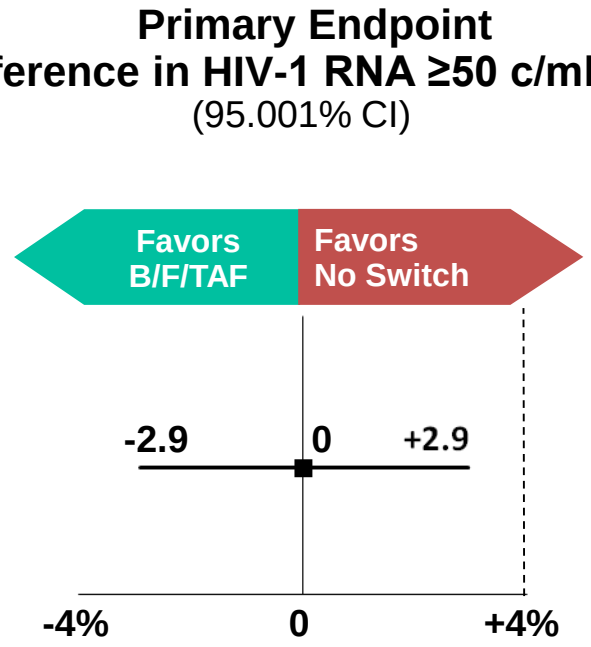
*Given without regard to food; †Given with food.

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. CROI 2018. Boston, MA. Poster 500.
ClinicalTrials.gov URL: https://clinicaltrials.gov/ct2/show/NCT02652624?term=1961&cond=HIV&rank=1 Accessed on February 25, 2018

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

Adverse Events (AEs) through Week 48

	B/F/TAF n=234	SBR n=236
Any grade AEs	66%	67%
AEs ≥ 5% in either arm		
Nasopharyngitis	8%	6%
Urinary tract infection	7%	2%
Upper respiratory tract infection	6%	6%
Headache	6%	6%
Vulvovaginal candidiasis	5%	4%
Drug-related AEs	9%	6%
Drug-related AEs (≥ 1%)*	None	Hypercholesterolemia (1%)
Discontinuations due to AEs	0	0

* B/F/TAF: Iron deficiency anemia, nausea, and vomiting (n=2) and SBR: upper abdominal pain (n=2)

- The majority of AEs were Grade 1 or 2
- Similar rates of Grade 3 to 4 AEs: B/F/TAF (5%) and SBR (6%)

B/F/TAF was well tolerated with no discontinuations due to AEs

Pregnancy Data through Week 48

	B/F/TAF n=5	SBR n=7
Protocol	Discontinue study drug	ART regimen at the investigator's discretion
Live birth	1	2 (1 with twins)
Elective terminations	2	0
Spontaneous abortions	0	2
Ongoing pregnancy	0	1
Pregnancy outcomes unknown	2	2

SBR: Stayed on Baseline Regimen

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

OUTLINE

- Linee guida
- Perché:
  - Comorbidità
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  - Gravidanza e PK/safety
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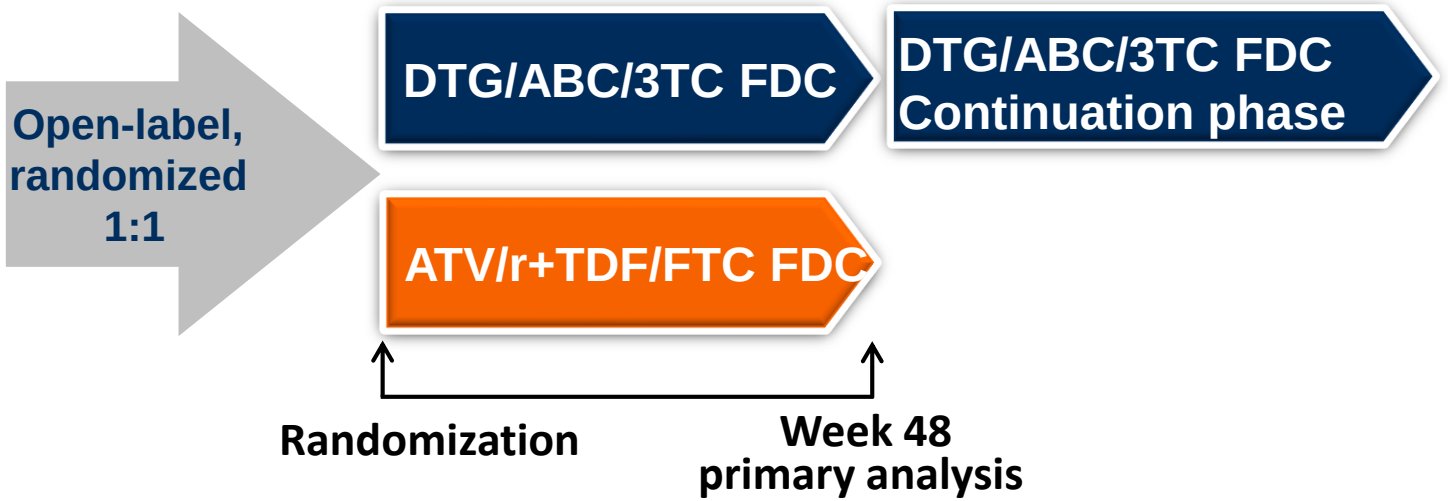
  TAF ABC/3TC/DTG D/C/F/T 2DR

ARIA: Study Design

Open-label randomised non-inferiority phase 3b study



- **Key eligibility criteria:** **women**, ART-naive, HLA-B*5701 negative, HIV-1 RNA >500 c/mL, hepatitis B negative
- **Stratification:** by HIV-1 RNA (≤ or >100,000 copies/mL), CD4+ count (≤ or >350 cells/mm^3)
- Women who became pregnant were withdrawn and, if possible, offered entry into a DTG/ABC/3TC pregnancy study
- **Primary endpoint:** proportion with HIV-1 RNA <50 c/mL at Week 48 using the FDA snapshot algorithm (-12% non-inferiority margin)

ART, antiretroviral therapy; FDA, US Food and Drug Administration; FDC, fixed-dose combination; HLA, human leukocyte antigen.

Orrell et al. AIDS 2016; Durban, South Africa. Slides THAB0205LB.

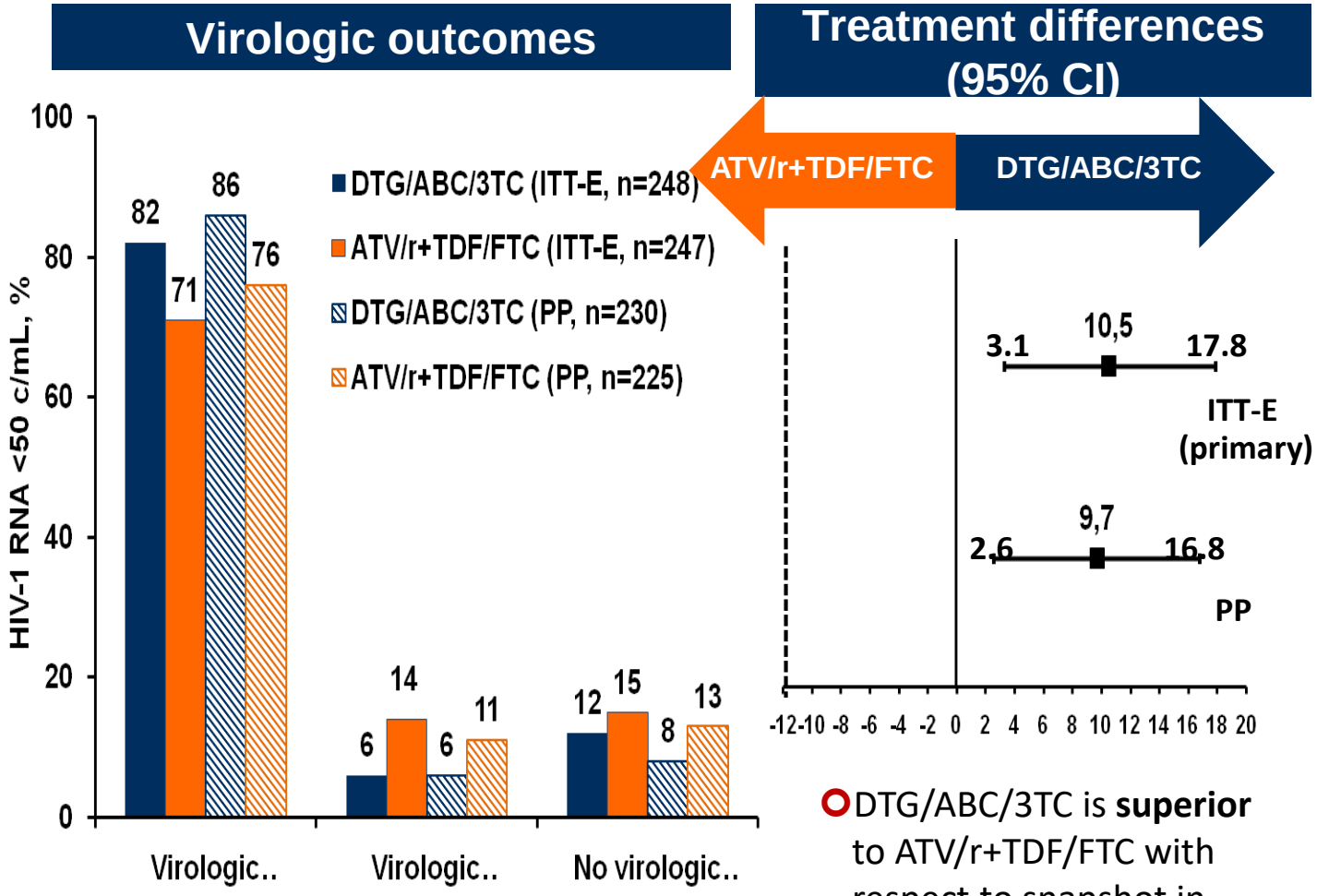
ARIA: Demographics and Baseline Characteristics

	DTG/ABC/3TC (n=248)	ATV/r +TDF/FTC (n=247)
Age, median (range), y	**37.5 (19-79)**	**37.0 (20-65)**
Race, n (%)		
African heritage	**102 (41)**	**108 (44)**
White	**115 (46)**	**107 (43)**
Asian	**22 (9)**	**23 (9)**
Hepatitis C, n (%)	**16 (6)**	**21 (9)**
CDC category, n (%)		
Asymptomatic	**210 (85)**	**208 (84)**
AIDS	**11 (4)**	**9 (4)**
HIV-1 RNA (log c/mL)	**4.48**	**4.44**
>100,000 (c/mL), n (%)	**69 (28)**	**66 (27)**
CD4+ cell count	**370**	**380**
<350 (cells/mm^3), n (%)	**130 (52)**	**123 (50)**

CDC, Centers for Disease Control.

Orrell et al. AIDS 2016; Durban, South Africa. Slides THAB0205LB.

Snapshot Outcomes at Week 48: ITT-E and PP Populations



- DTG/ABC/3TC is **superior** to ATV/r+TDF/FTC with respect to snapshot in the ITT-E (<50 c/mL) at Week 48, ***P*=0.005**

CI, confidence interval; ITT-E, intent-to-treat exposed; PP, per protocol.

Orrell et al. AIDS 2016; Durban, South Africa. Slides THAB0205LB.

Snapshot Outcomes at Week 48: ITT-E

	DTG/ABC/3TC (n=248)	ATV/r+TDF/FTC (N=247)
Virologic response	203 (82%)	176 (71%)
Virologic non-response	16 (6%)	35 (14%)
Data in window not below threshold	4 (2%)	16 (6%)
Discontinued while VL not <50*	12 (5%)	19 (8%)
No virologic data	29 (12%)	36 (15%)
Discontinued study due to AE or death	9 (4%)	18 (7%)
Discontinued study for other reasons	15 (6%)	14 (6%)
Missing data during window but on study	5 (2%)	4 (2%)

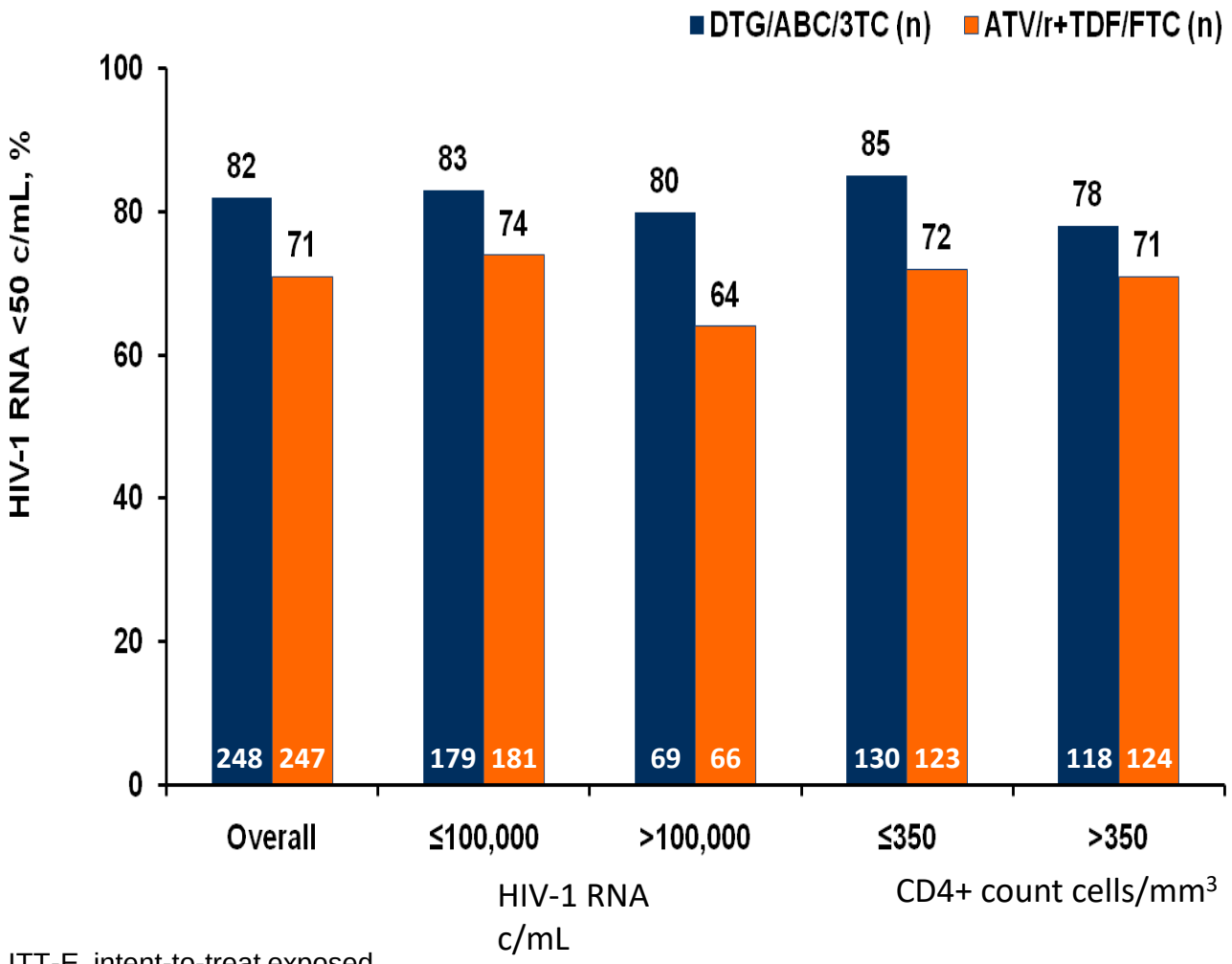
Differences in response rates driven by Snapshot virologic non-response and lower rates of both discontinuations due to AEs in the DTG/ABC/3TC group.

*Includes categories: Discontinued for lack of efficacy and Discontinued for other reason while not below threshold

AE, adverse, event; ITT-E, intent-to-treat exposed

Orrell et al. AIDS 2016; Durban, South Africa. Slides THAB0205LB.

Snapshot Outcomes by Baseline Randomization Strata at Week 48: ITT-E



ITT-E, intent-to-treat exposed.

Orrell et al. AIDS 2016; Durban, South Africa. Slides THAB0205LB.

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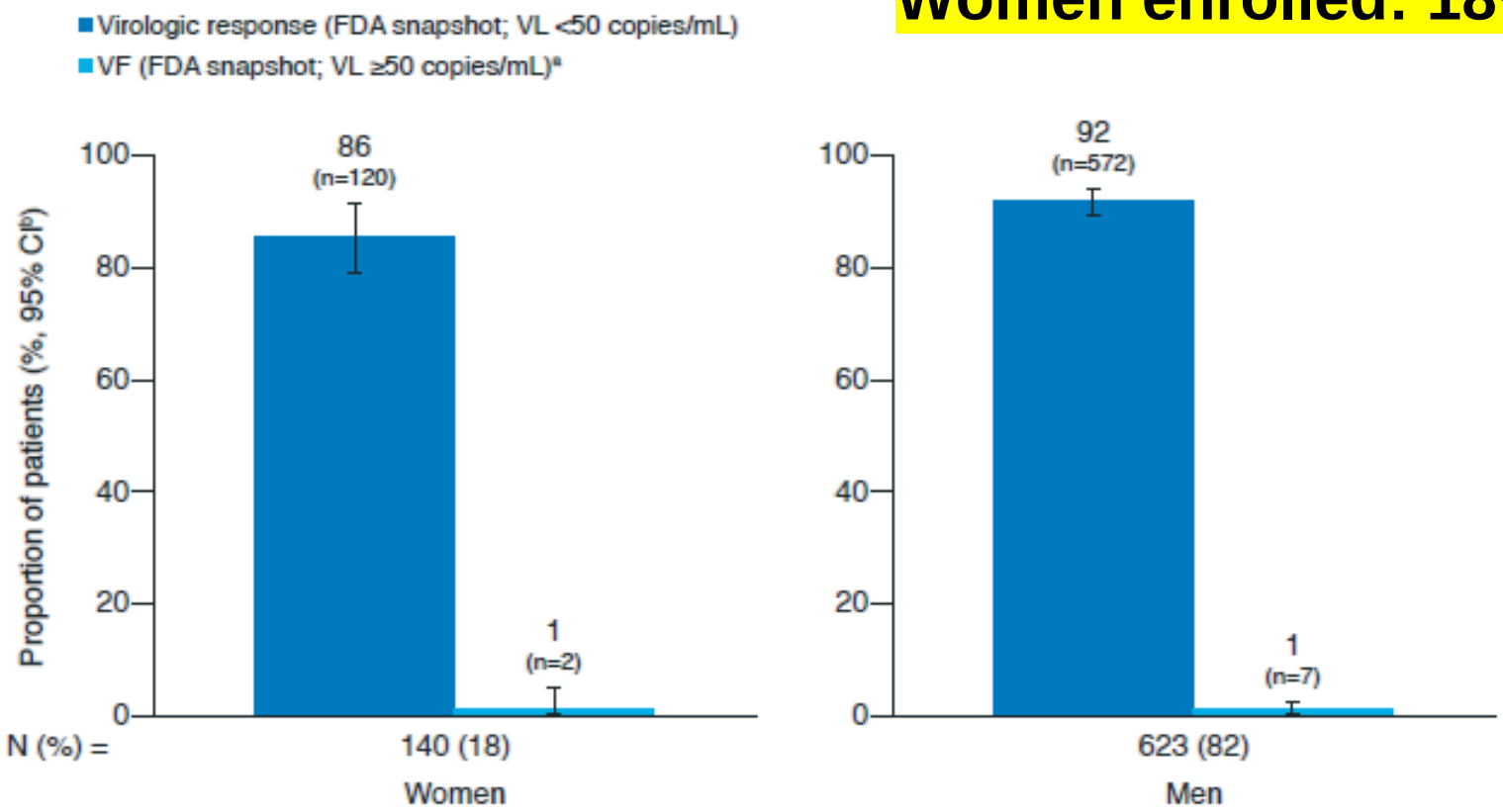
EMERALD Week 96 Women: Virologic Outcomes at Week 96 (FDA Snapshot) in the D/C/F/TAF Arm by Gender

Women enrolled: 18%



- A high sustained Week 96 virologic response rate of 86% was maintained in the D/C/F/TAF arm in women (men: 92%) with a low VF rate of 1% in both genders

[a]VF was defined as last VL in the Week 96 window ≥50 copies/ml, or discontinuations for efficacy reasons, or premature discontinuations not due to efficacy, adverse events or death with a last VL ≥50 copies/ml; [b]Two-sided Exact Clopper-Pearson 95% CI.
D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; VF, virologic failure; VL, viral load; CI, confidence interval.

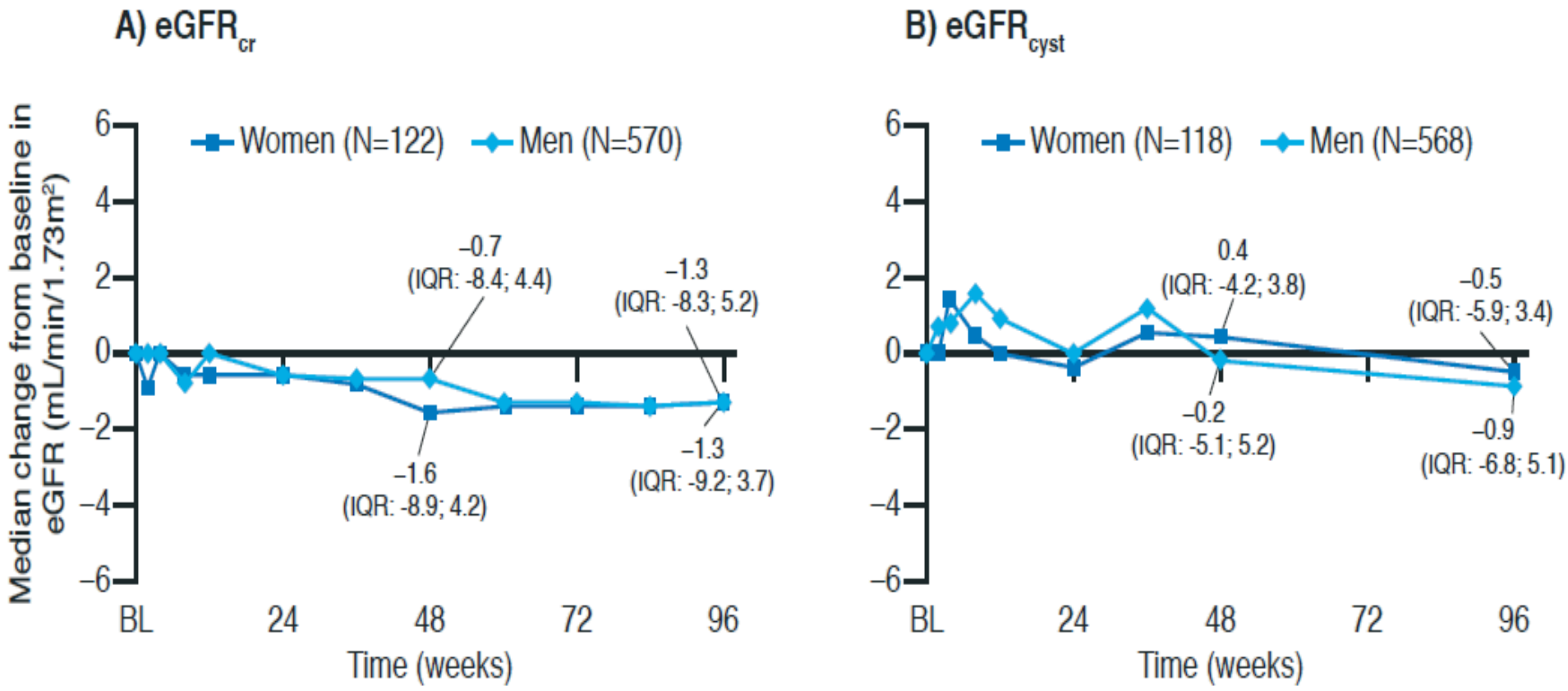
EMERALD Week 96 Women: Safety Results

Incidence, n(%)	Women (N=140)	Men (N=623)
≥1 AE, any grade	122 (87)	568 (91)
Study drug-related AEs	33 (24)	132 (21)
Study drug-related Grade 3 or 4 AEs	2 (1)	12 (2)
≥1 serious AE	13 (9)	53 (9)
Study drug-related serious AEs	0	2 (<1)
≥1 AE leading to discontinuation	3 (2)	14 (2)
Fatal AEs[a]	0	3 (<1)

- Rates of study drug-related Grade 3 or 4 and serious AEs and discontinuations due to AEs were low and similar in women and men in the D/C/F/TAF arm
- The most common AEs (≥10% overall D/C/F/TAF arm through 96 weeks) were URTI (16% both genders), viral URTI (14% women; 13% men) diarrhea (8% women; 11% men), headache (16% women; 9% men) and back pain (9% women; 10% men)

[a]Two cases of myocardial infarction (one in a patient who was a smoker with ongoing medical history of hyperlipidemia and hypertension, and one in a patient with ongoing medical history of obesity and hypertension), and one case of metastatic pancreatic cancer
D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; AEs, adverse events;
URTI, upper respiratory tract infection.

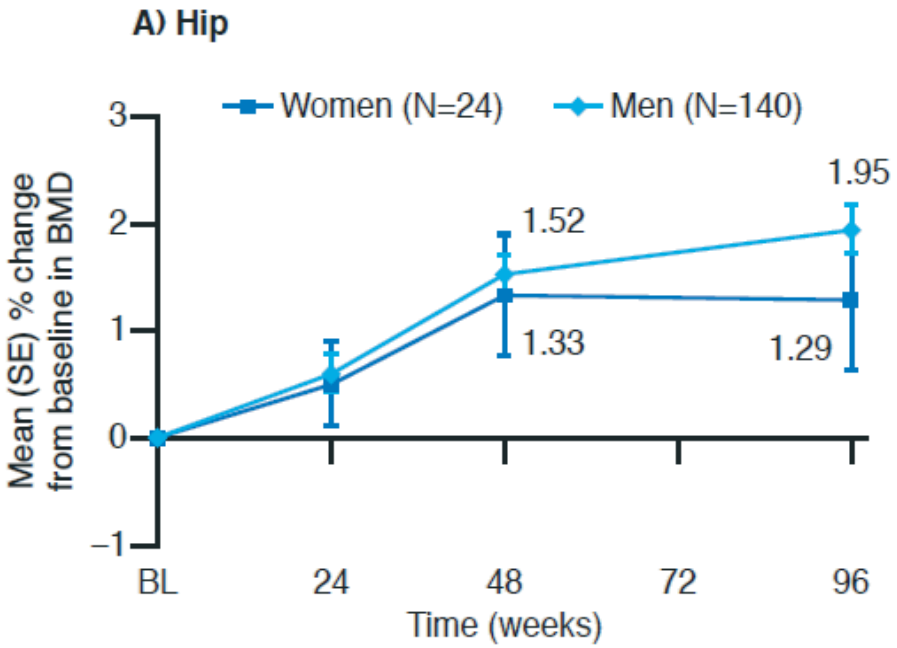
EMERALD Week 96 Women: Median Change form Baseline to Week 96 in $eGFR_{cr}$ and $eGFR_{cyst}$ in the D/C/F/TAF Arm by Gender

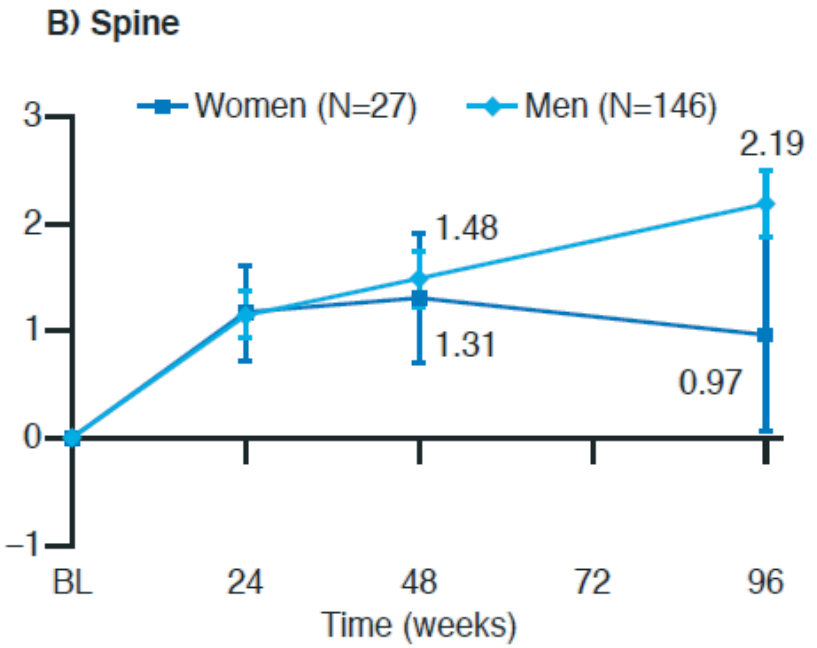


- Median change in estimated Median change in eGFR remained stable through Week 96 for both genders and no cases of Fanconi Syndrome or subclinical PRT were detected

eGFRcr and eGFRcyst (both based on serum levels and CKD-EPI formula); GFR normal range: 90–120 mL/min/1.73m2; N is the number of evaluable women or men at Week 96
D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; PRT, proximal renal tubulopathy; $eGFR_{cr}$, estimated glomular filtration rate creatinine; eGFR, estimated glomular filtration rate cystatin C; IQR, interquartile range; BL baseline; CKD, chronic kidney disease.

EMERALD Week 96 Women: Mean (SE) Percent Change from Baseline to Week 96 in A) Hip and B) Spine BMD in the D/C/F/TAF Arm by Gender

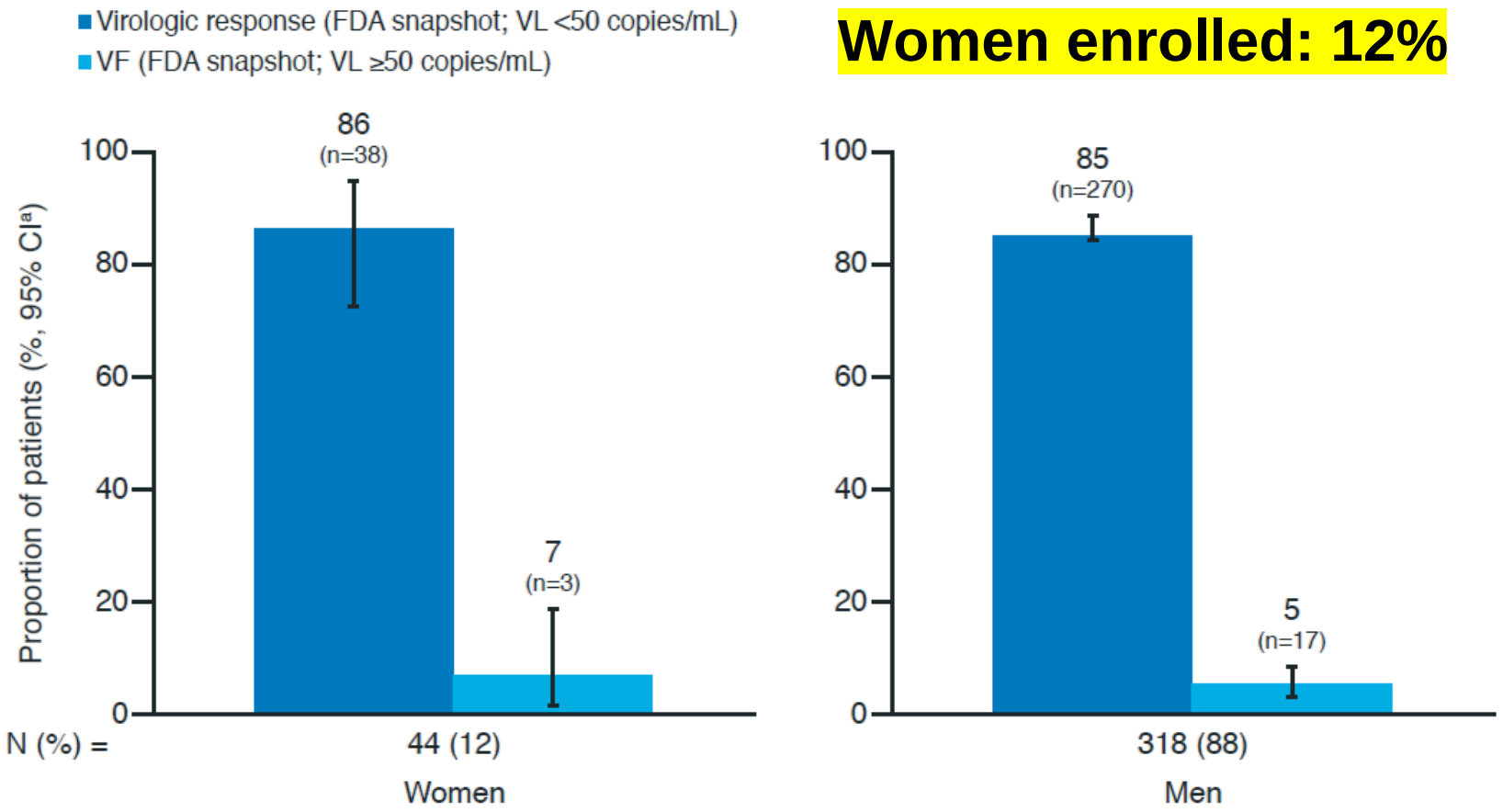




- Numerical increases in hip and spine BMD through Week 96 versus baseline were observed for both genders, with overall numerically smaller increases in women; femoral neck BMD changes followed the same pattern at Week 96 (women: +0.05%; men: +1.61%)

BMD was evaluated in a substudy of EMERALD. N is the number of evaluable women or men at Week 96.
D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; BMD, bone mineral density;
SE, standard error.

AMBER Week 96 Women: Virologic Outcomes at Week 96 (FDA Snapshot) in the D/C/F/TAF Arm by Gender (ITT Population)



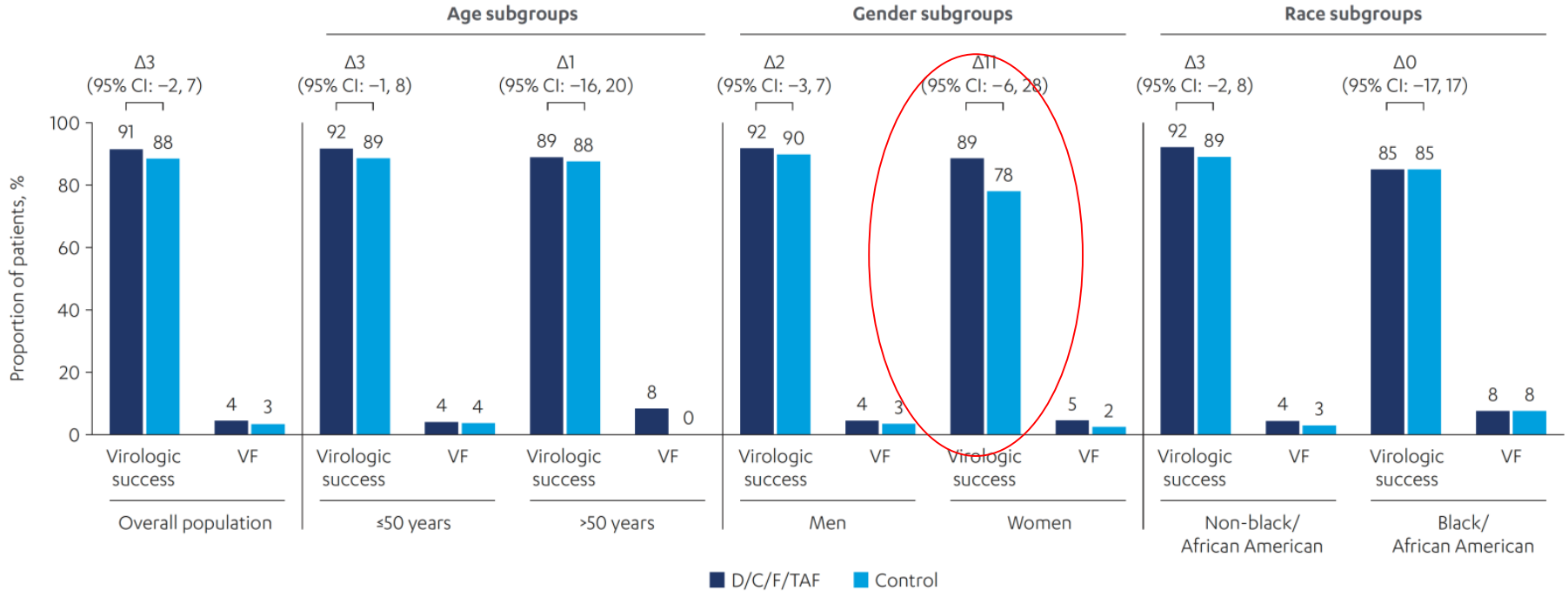
Women enrolled: 12%

- A high proportion of women in the D/C/F/TAF arm had a virologic response (86%) at Week 96 (men: 85%) and a low proportion had VF (women: 7%; men: 5%)

[a]Two-sided Exact Clopper-Pearson 95% CI.
D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; VF, virologic failure; ITT, intent-to-treat; VL, viral load; CI, confidence interval.

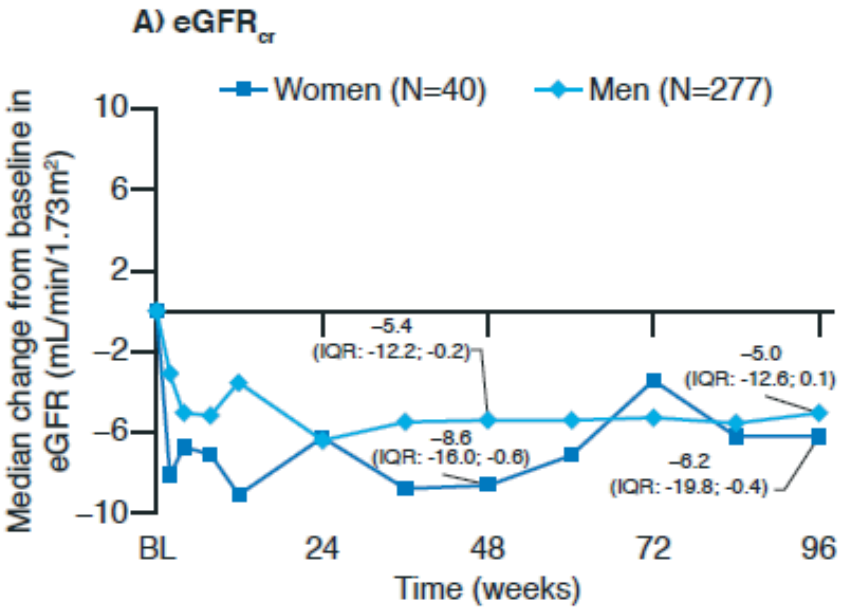
AMBER: Virologic response at Week 48 by age, gender and race subgroups (FDA Snapshot; VL<50 c/mL) (ITT)

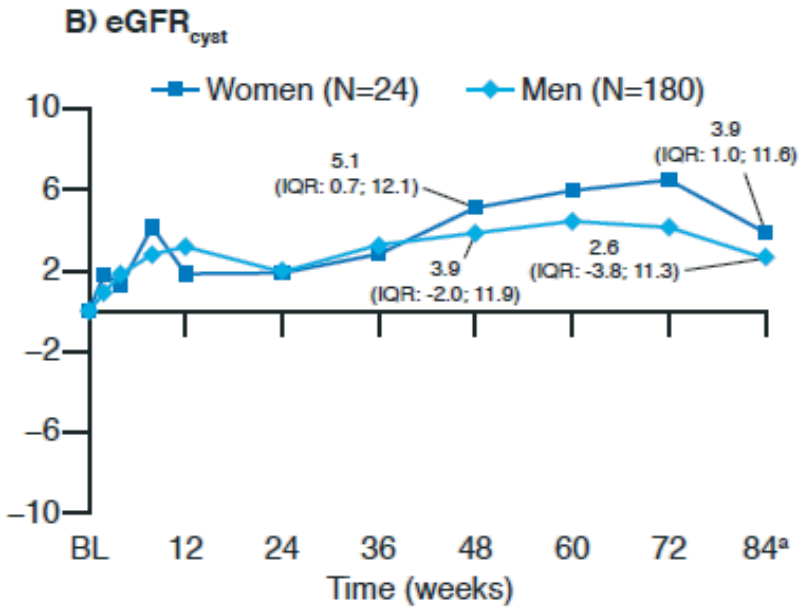
Figure 2. Virologic response at Week 48.*



VF, virologic failure.
*Overall, 15 (4%) patients treated with D/C/F/TAF and 30 (8%) patients treated with control did not have virologic response data at Week 48. For each subgroup, patients with missing data in the D/C/F/TAF and control treatment groups, respectively, were as follows: 4% and 8% of those aged ≤50 years, 3% and 13% aged >50 years, 4% and 7% men, 7% and 20% women, 4% and 8% non-black/African American, and 8% and 8% black/African American.

AMBER Week 96 Women: Median Change from Baseline to Week 96 in A)eGFRcr B)eGFRcyst in the D/C/F/TAF Arm by Gender

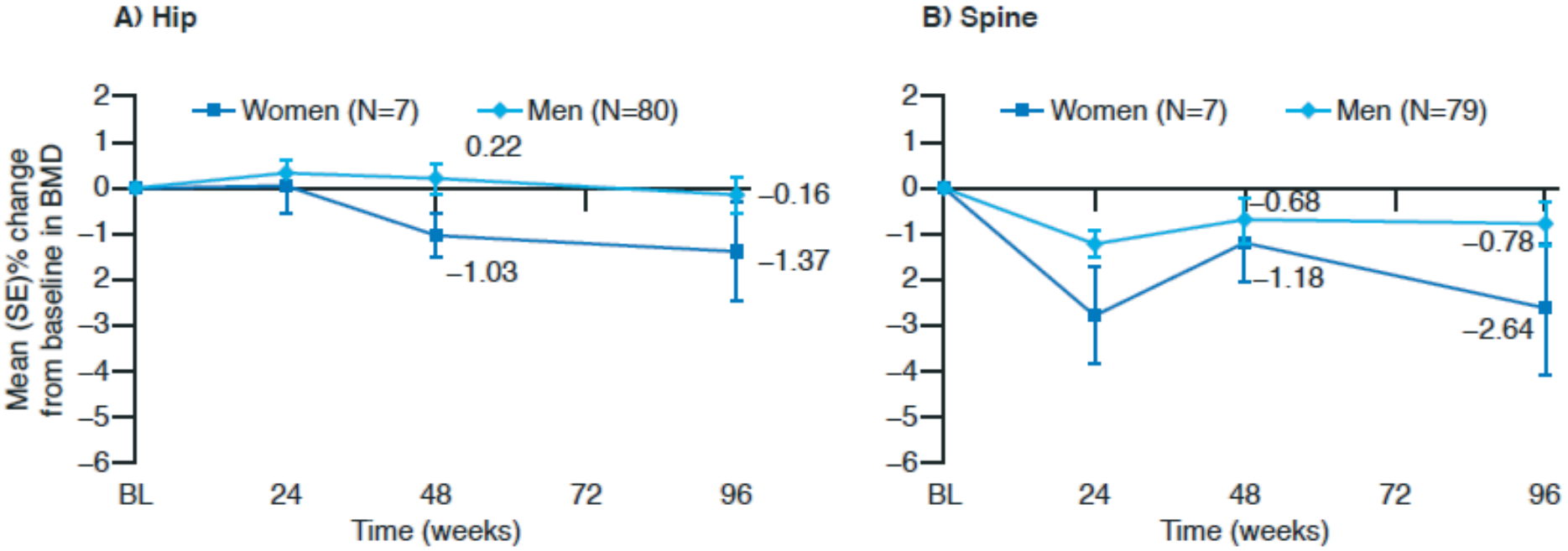




- No clinically relevant changes in eGFR and no cases of Fanconi Syndrome or subclinical PRT were observed through Week 96 for either gender

Baseline eGFRcr = eGFR based on creatinine and eGFRcyst = eGFR based on cystatin C (both based on serum levels and CKD-EPI formula); IQR.
GFR normal range: 90–120 mL/min/1.73m2; [a]Cystatin C was not routinely collected during the open-label phase so only 22 patients had results for the Week 96 time point; N is the number of evaluable women or men at A) Week 96 or B) Week 84
D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; BL, baseline; IQR, inter-quartile range; $eGFR_{cr}$, estimated glomular filtration rate creatinine; eGFR, estimated glomular filtration rate cystatin; GRF, glomular filtration rate;
PRT, proximal renal tubulopathy.

AMBER Week 96 Women: Mean (SE) Percent Change from Baseline to Week 96 in A) Hip and B) Spine BMD in the D/C/F/TAF Arm by Gender



- At Week 48, mean change in BMD at each site was statistically favorable for the D/C/F/TAF arm versus the control arm
- In the D/C/F/TAF arm through Week 96, there were small decreases in hip and lumbar spine BMD, with overall numerically greater decreases in women; femoral neck BMD changes followed the same pattern at Week 96 (women: −2.27%; men: −1.17%)

BMD was evaluated in a substudy of AMBER; N is the number of evaluable women or men at Week 96.
D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; BL, baseline; BMD, bone mineral density; SE, standard error.

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  TAF ABC/3TC/DTG D/C/F/T 2DR

Efficacy of the Two-Drug Regimen of Dolutegravir Plus Lamivudine (DTG+3TC) vs Dolutegravir Plus Tenofovir/Emtricitabine (DTG+TDF/FTC) at W48 in Antiretroviral Naive Women: GEMINI Studies Subgroup Analysis

20

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Introduction

- Two-drug regimens (2DRs) are being evaluated against standard 3-drug regimens for their potential to reduce cumulative drug exposure during life-long antiretroviral therapy in patients with HIV-1 infection
- In the GEMINI studies, the 2DR of DTG+3TC was recently shown to have noninferior virologic efficacy compared with DTG+TDF/FTC at 48 weeks in treatment-naive adults[1]
- We present a secondary analysis evaluating the efficacy and safety outcomes in women from the GEMINI studies

Methods

- **Study design:** Phase III, randomized (1:1), double-blind, parallel-group
  - Participants received either DTG+3TC (N=716) or DTG+TDF/FTC (N=717)
- **Stratification:** By screening plasma HIV-1 RNA (≤100,000 c/mL vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm^3)
- **Key eligibility criteria:** Age ≥18 years; antiretroviral therapy (ART) naive (≤10 days of prior ART); no evidence of pre-existing major resistance-associated mutations; no hepatitis B virus infection; HIV-1 RNA 1000 to 500,000 c/mL
- **Primary endpoint:** Proportion with plasma HIV-1 RNA <50 c/mL at Week 48 using Snapshot algorithm; −10% non-inferiority margin
- **Subgroup analyses:** Snapshot outcomes and adverse event (AE) frequencies by demographics and baseline HIV-1 RNA and CD4+ cell count
- **Statistical analysis:** For the primary endpoint, estimates and confidence intervals (CIs) were based on a stratified analysis using Cochran-Mantel-Haenszel weights
  - The subgroup analyses were unadjusted

Results

Study population

- 1433 adults from 21 countries were randomized and treated in GEMINI-1 and -2 (Table 1)

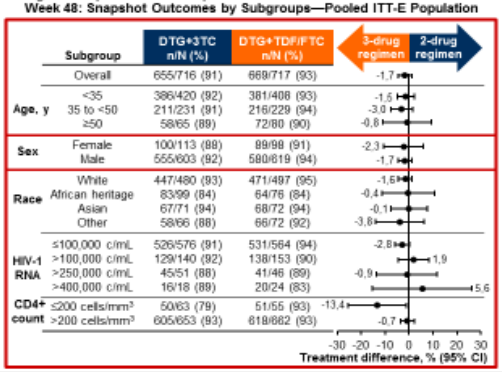
Table 1. Demographics and Baseline Characteristics: Pooled ITT-E Population

Characteristic	DTG+3TC (N=716)	DTG+TDF/FTC (N=717)
Age, median (range), y	32.0 (18-72)	33.0 (18-70)
Female, n (%)	113 (16)	98 (14)
Race, n (%)		
African heritage	99 (14)	76 (11)
Asian	71 (10)	72 (10)
White	480 (67)	497 (69)
Other	66 (9)	72 (10)
HIV-1 RNA, median (range), $\log_{10}$ c/mL	4.43 (1.59-6.27)	4.46 (2.11-6.37)
>100,000, n (%)	140 (20)	153 (21)
CD4+ cell count, median (range), cells/mm^3	427.0 (19-1399)	438.0 (19-1497)
≤200, n (%)	63 (9)	55 (8)

Efficacy

- Subgroup analyses of efficacy based on baseline disease and demographic characteristics were generally consistent with overall study results (Figure)

Figure. Proportion of Participants With Plasma HIV-1 RNA <50 c/mL at Week 48: Snapshot Outcomes by Subgroups—Pooled ITT-E Population



- 211 women were included and exposed to DTG-based regimens, representing 15% of the study population
- 113 (16%) women were included in the DTG+3TC arm and 98 (14%) in the DTG+TDF/FTC arm
- 100 (88%) of 113 women taking DTG+3TC achieved plasma HIV-1 RNA <50 c/mL at Week 48 compared with 89 (91%) of 98 women in the DTG+TDF/FTC group (difference in proportion, −2.3% [95% CI, −10.5% to 5.9%])

Safety

- Overall rates of AEs were similar between arms, with low rates of withdrawals due to AEs in both arms (DTG+3TC, 15/716 [2%] vs DTG+TDF/FTC, 16/717 [2%])
- More participants taking DTG+TDF/FTC reported drug-related AEs (169/717 [24%]) than did those taking DTG+3TC (126/716 [18%])
- The frequency of AEs was generally similar across subgroups (Table 2)
- In women, AE frequency was comparable between arms
- Results of efficacy and safety subgroup analyses were similar in the individual studies compared with pooled results

Table 2. Adverse Events Frequency by Subgroup: Pooled Safety Population

Variable	Subgroup	DTG+3TC n/N (%)	DTG+TDF/FTC n/N (%)
Overall	—	543/716 (76)	579/717 (81)
Age, y	<35	312/420 (74)	326/408 (80)
	35 to <50	186/231 (81)	186/229 (81)
	≥50	45/65 (69)	67/80 (84)
Sex	Female	82/113 (73)	68/98 (69)
	Male	461/603 (76)	511/619 (83)
Race, n (%)	White	352/480 (73)	390/497 (78)
	African heritage	78/99 (79)	65/76 (86)
	Asian	57/71 (80)	58/72 (81)
	Other	56/66 (85)	66/72 (92)
Baseline HIV-1 RNA, c/mL	≤100,000	442/576 (77)	449/564 (80)
	>100,000	101/140 (72)	130/153 (85)
Baseline CD4+ cell count, cells/mm^3	≤200	43/63 (68)	48/55 (87)
	>200	500/653 (77)	531/662 (80)

Conclusions

- In GEMINI-1 and -2, DTG+3TC demonstrated noninferior virologic efficacy compared with DTG+TDF/FTC in treatment-naive adults at Week 48
- DTG+3TC demonstrated similar virologic efficacy to DTG+TDF/FTC in treatment-naive women
- Both regimens were well tolerated, with low rates of treatment discontinuation due to adverse events
- These results demonstrate that DTG+3TC is an option for initial treatment of HIV-infected patients across a spectrum of disease characteristics and patient populations
- The studies are ongoing to explore the long-term durability and safety of the DTG+3TC 2DR compared with a standard 3-drug regimen

Acknowledgments

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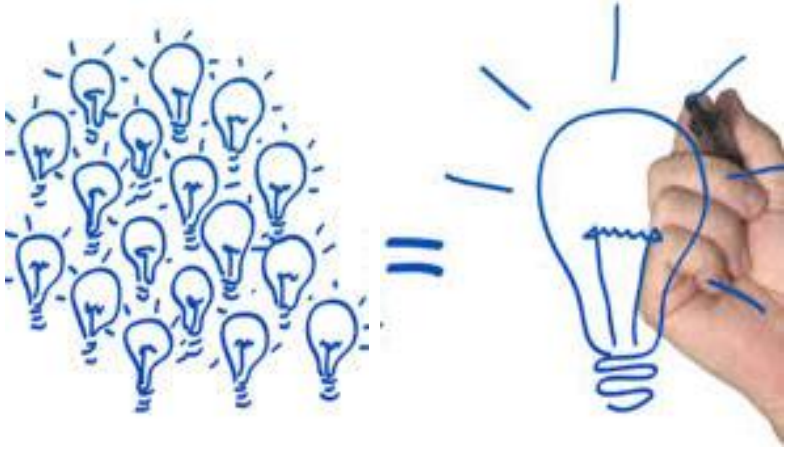
Reference

1. Cahn P, Madero JS, Arribas J, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate/emtricitabine in antiretroviral-naive adults with HIV-1 infection: Week 48 results from two randomised, double-blind, phase III, non-inferiority studies (GEMINI-1 and GEMINI-2). *Lancet*. 2019;393:143-155.

2° INCONTRO
INHIMEGE
Aspetti terapeutici e di prevenzione nell'universo femminile HIV-positivo

16 OTTOBRE 2019
NAPOLI
Azienda Ospedaliera dei Colli
Aula Conferenze D. Cotugno

Parametri di scelta della terapia antiretrovirale nel genere femminile



POPOLAZIONE FEMMINILE

Grazie per l'attenzione!

OSPEDALI DEI COLLI
MONALDI - COTUGNO - C.T.O.