Azienda Ospedaliera
SAN PAOLO
POLO UNIVERSITARIO

Donne e infezione da HIV: una popolazione speciale?

Teresa Bini

Clinica di Malattie Infettive
Ospedale "San Paolo"
Università di Milano

Global summary of the AIDS epidemic | 2009

Number of people living with HIV	Total	33.3 million [million– million]
	Adults	30.8 million [million– million]
	Women	15.9 million [million– million]
	Children (<15 years)	2.5 million [1.6 million–3.4 million]
People newly infected with HIV in 2009	Total	2.6 million [2.3 million–2.8 million]
	Adults	2.2 million [2.0 million–2.4 million]
	Children (<15 years)	370 000 [230 000–510 000]
AIDS deaths in 2009	Total	1.8 million [1.6 million–2.1 million]
	Adults	1.6 million [1.4 million–1.8 million]
	Children (<15 years)	260 000 [150 000–360 000]

UNAIDS

HIV e differenze di genere: possibili discriminanti

- Modalità di infezione
- Accesso alle cure
- Aderenza alla terapia
- Progressione di malattia/outcome del trattamento
- Tossicità/interazioni farmacologiche
- Comorbidità/morbidità legata all'invecchiamento
- Maternità

Rischio di trasmissione dell'infezione

Type of exposure (From a source known as HIV positive)	Risk of HIV transmission per exposure
Accidental needle stick	0.2%-0.4%
Mucosal membrane exposure	0.1%
Receptive Oral Sex	Varied from 0 to 6.6%
Insertive vaginal sex	≤ 0.1%
Insertive anal sex	≤ 0.1%
Receptive vaginal sex	0.01%-0.15 %
Receptive anal sex	≤ 3%
Sharing IDUs needle	0.7%
Transfusion	90-100%

Higher viral load and STIs increase transmission risk

Women, girls, gender equality and HIV

Global epidemiological data

- Women account for 50% of people living with HIV.[i]
- Globally, young women aged 15-24, are most vulnerable to HIV with infection rates twice as high as in young men, and accounting for 22% of all new HIV infections.[ii]
- HIV is the leading cause of death of women of reproductive age.[iii]
- In the absence of HIV, maternal mortality worldwide would be 20% lower[iv].

CDC: Prevention Challanges

- Most women are infected with HIV through **heterosexual sex**. Some women become infected because they may be unaware of a male partner's risk factors for HIV infection or have a lack of HIV knowledge and lower perception of risk. Relationship dynamics also play a role. For example, some women may not insist on condom use because they fear that their partner will physically abuse or leave them.

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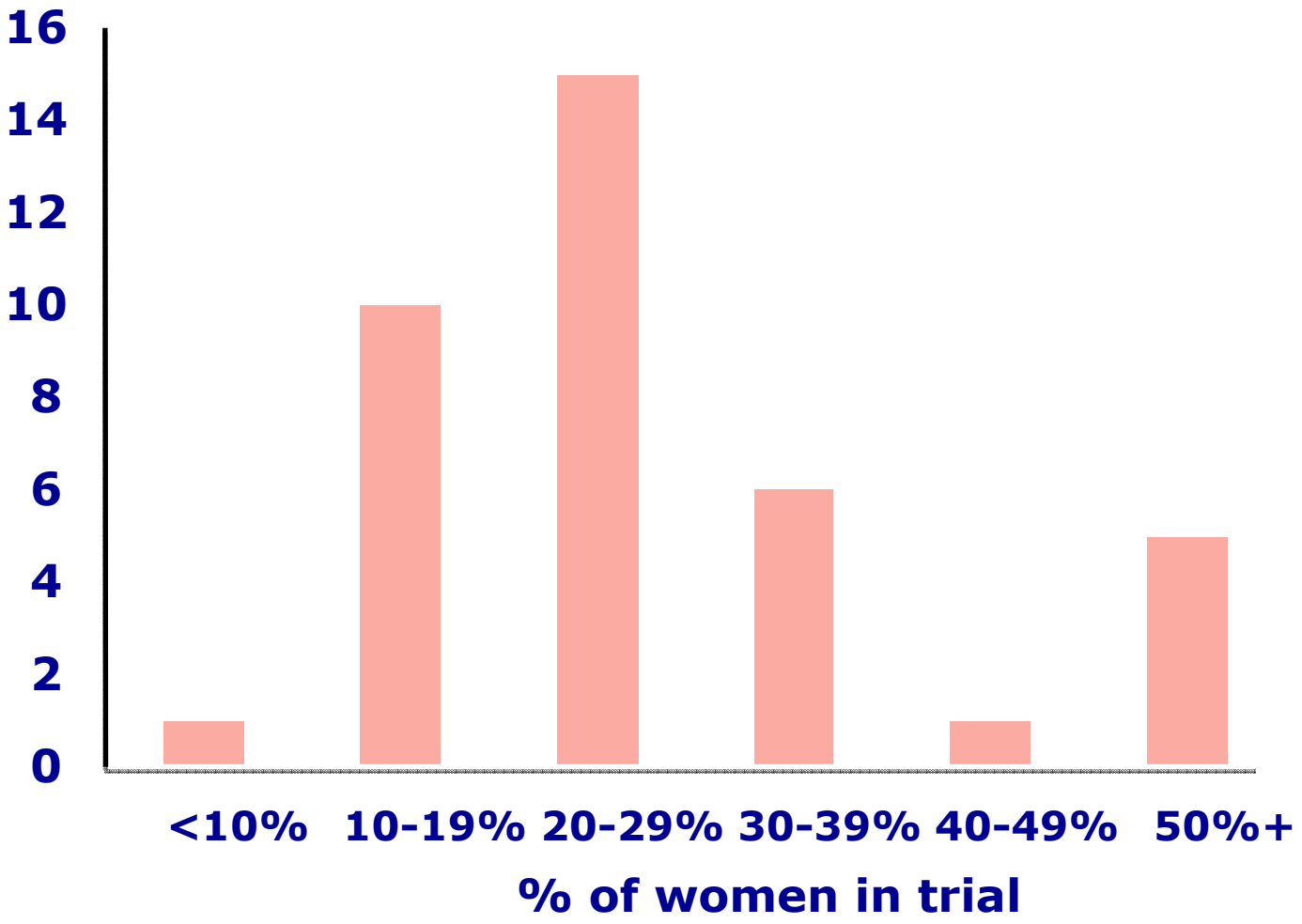
Accesso alle cure

- Negli U.S.A. l'accesso alle cure può essere difficoltoso a causa di mancanza di integrazione sociale, povertà, depressione, difficoltà nella funzione genitoriale; tutti questi fattori possono ritardare l'accesso alle cure nella popolazione femminile.
- In Italia ed in Europa l'assistenza è gratuita, ma sono possibili discriminazioni, soprattutto nei migranti e soprattutto se donne.

Pochi studi su donne sieropositive

Number of articles that assess the impact of specific sex differences of HAART on viro-immunological and clinical parameters during HAART

(Mar 02-Feb 07)



Nicastri et al, Journal of Antimicrobial Chemotherapy, 2007

Accesso ai clinical trials su HIV e HAART

Trials on naive population	women %
ACTG 5095	19
ACTG 5142	20
FIRST	20.6
GS934	13.5
GS903	25.5
SOLO	26
KLEAN	22
Trials on salvage therapy	**women %**
POWER	11.5
RESIST	9
TORO	10

Accesso ai clinical trials su HIV e HAART

Accettare l'arruolamento in Studi Clinici controllati per poter contribuire a valutare meglio l'impatto e gli effetti collaterali della HAART sulle donne

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Fattori predittivi di aderenza alla ARV (British Columbia Cohort, Vancouver)

Solo il 57% degli 886 pazienti mostra una aderenza > 95% (mediana del tempo di ARV:14 mesi)

Nell'analisi multivariata l'aderenza risulta significativa (p< 0.001) rispetto a:

Age	AOR 1.33 (95% CI 1.12-1.57)
[every 10 years more]	
AIDS at baseline	AOR 2.28 (95% CI 1.44-3.61)
Male gender	AOR 1.96 (95% CI 1.28-3.01)
Medical experience	AOR 1.45 (95%CI 1.20-1.74).
[every 100 HIV pts more]	
IVDU	AOR 0.50 (95% CI 0.36-0.71).

da: Montessori et al 7th CROI S Francisco 2000 abs 72

STUDIO APROCO: cause di non aderenza alla terapia antiretrovirale

	OR (95% CI)	P
Gender: M *vs* F	1.02 (0.52-1.99)	-
Age	1.05 (1.01-1.07)	0.04
Naïve to ART	0.51 (0.28-0.93)	0.01
IDU HIV-infected	0.82 (0.38-1.77)	-
Homeless	2.79 (1.19-6.57)	0.001
Low social support	2.13 (1.20-3.45)	0.001
Alcohol use at M4	1.07 (1.03-1.11)	0.01
N of symptoms at M1	1.93 (1.11-3.36)	0.001

APROCO study Group, JNI, Lyon, June 2000

HIV e differenze di genere: possibili discriminanti

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Diversa risposta al trattamento?

Le donne possono rispondere diversamente alla HAART per vari motivi:

- Diversa massa corporea e distribuzione del tessuto adiposo
- Diverso metabolismo dei farmaci
- Azione ormonale:
  - Naturale
  - Terapia ormonale sostitutiva
  - Gravidanza
  - Utilizzo di contraccettivi orali
- Inizio più tardivo della HAART

The Body. Available at: http://www.thebody.com/women/resource/mainOverview.html. Accessed July 9, 2007

Potenziali cause di diverso outcome terapeutico

Fattori sociali ed economici:

- La donna è spesso "caregivers" per altri
- Stigma
- Povertà

Effetti avversi della terapia:

- Depressione
- Cambiamento nel profilo lipidico
- Redistribuzione del grasso corporeo

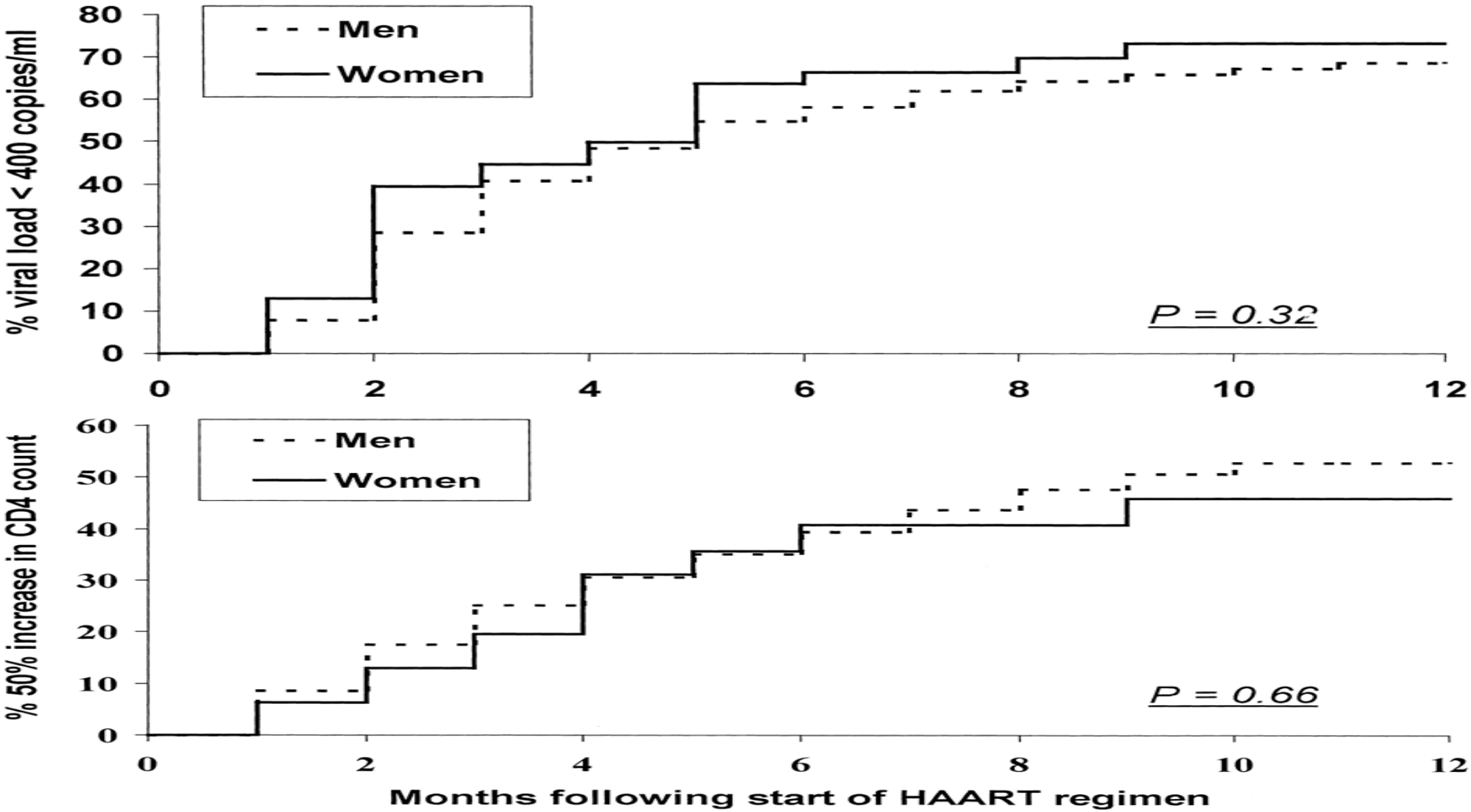
Italian Cohort
I C O N A
Naive Antiretroviral

Valore di HIV-1 RNA (media, mediana log10 copie/ml) secondo le caratteristiche demografiche dei pazienti alla prima osservazione

Characteristic		Baseline plasma HIV RNA concentrations		
		Median copies/mL	Mean log10	p-value
Gender				
Women	(n=159)	7,548	3.84	0.02
Men	(n=221)	13,546	4.04	
Age (years)				
<30		10,000	4.03	0.41
30-35		10,200	3.94	
>35		8,345	3.88	
Modality of HIV transmission				
IDU				
Heterosexuals		10,415	3.97	0.38
		8,606	3.93	

Rezza et al, JAIDS 2000

Risposta immunologica e virologica alla HAART



Mocroft at al, JAMA 2000

Efficacy, Safety and Tolerability of Lopinavir/ritonavir (LPV/r) in HIV-Infected Women: Results of a Meta-Analysis of 7 Prospective, Randomized Clinical Trials (RCTs) Through 48 Weeks

Ashwaq Hermes, Linda Fredrick, Mary Pasley, Roger Trinh, Marisol Martinez, Michael Norton
Abbott, Abbott Park, IL
Corresponding author: Michael Norton - Abbott, 200 Abbott Park Road, Building AP30-3, Abbott Park, IL 60064
1st International Workshop on HIV & Women *from Adolescence through Menopause* • Washington DC • January 10 - 11, 2011

Figure 1. Subjects That Met Meta-analysis Criteria

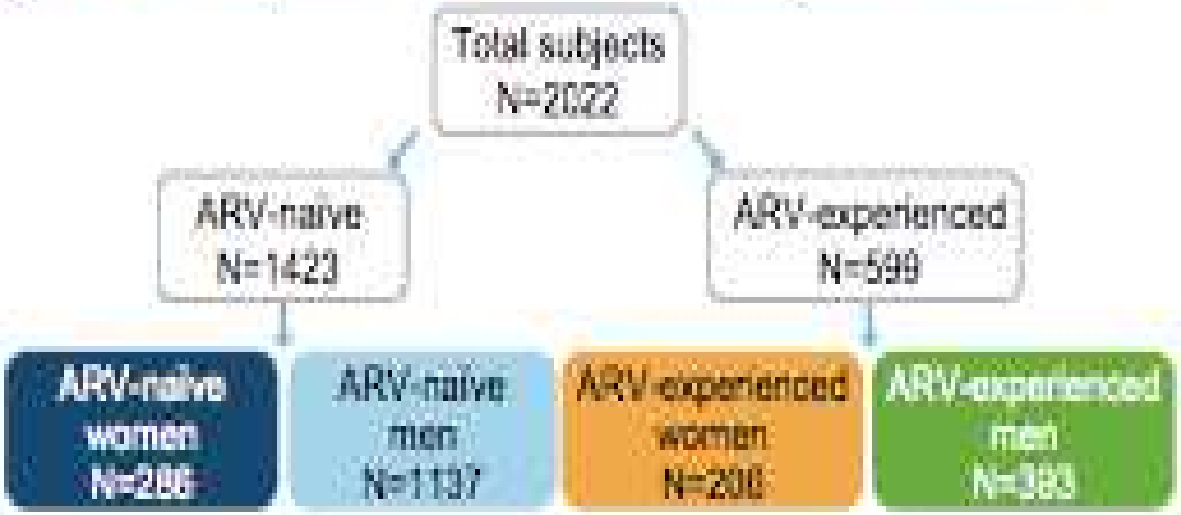


Figure 2A. Proportion of ARV-naïve Subjects with HIV-1 RNA <50 Copies/mL through Week 48 by Gender (ITT NC=F and OD)

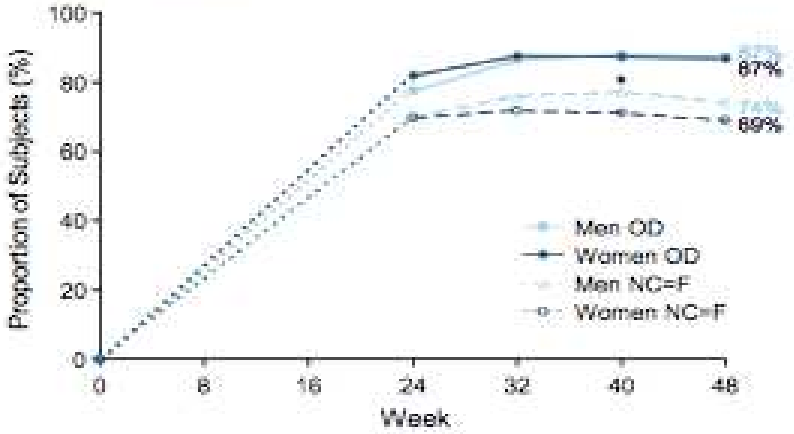


Figure 2B. Proportion of ARV-experienced Subjects with HIV-1 RNA <50 Copies/mL through Week 48 by Gender (ITT NC=F and OD)

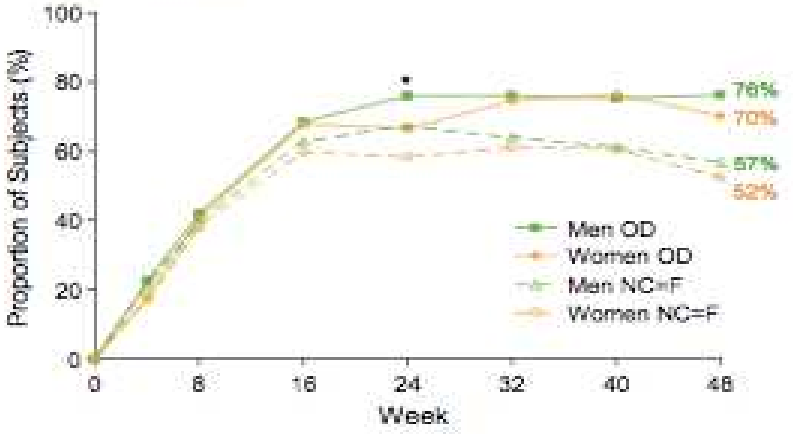


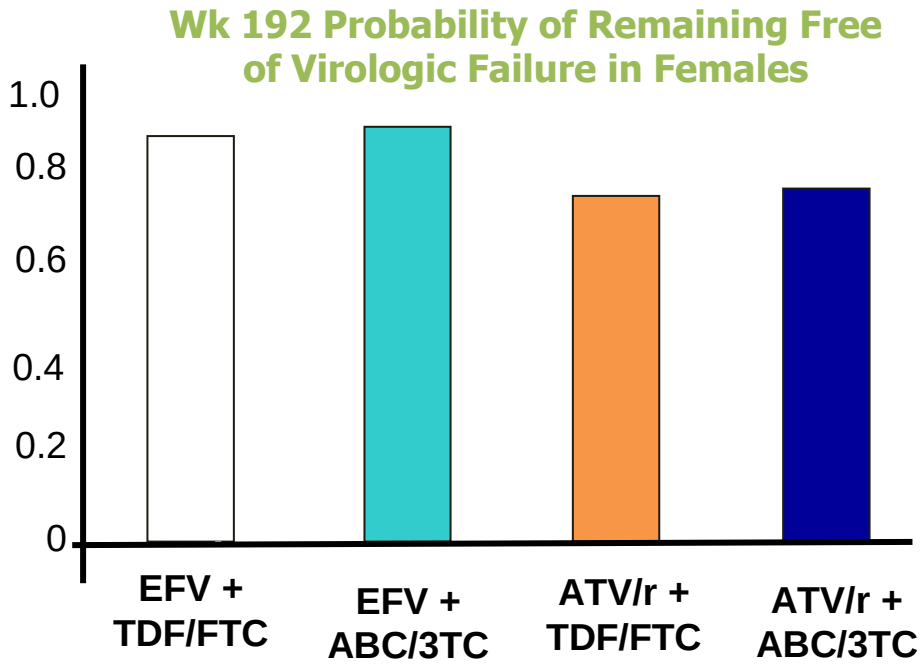
Table 3. Moderate-Severe Adverse Events Possibly Related to LPV/r with ≥ 2.0% Incidence in Any Group

Variable	ARV-naïve women N=286	ARV-naïve men N=1137	ARV-experienced women N=205	ARV-experienced men N=393
Any adverse event, n (%)	98 (34.3)	397 (34.9)	58 (28.2)	100 (25.4)
Diarrhea	34 (11.9)	182 (16.0)	26 (12.6)	49 (12.5)
Nausea	28 (9.8)	72 (6.3)	13 (6.3)	17 (4.3)
Vomiting	19 (6.6)	27 (2.4)*	6 (2.9)	8 (2.0)
Dyspepsia	6 (2.1)	8 (0.7)*	2 (1.0)	2 (0.5)
Upper abdominal pain	1 (0.3)	8 (0.7)	5 (2.4)	3 (0.8)
Fatigue	5 (1.7)	29 (2.6)	0	0
Headache	3 (1.0)	24 (2.1)	0	1 (0.3)

*Statistically significantly different compared to women ($P<0.05$) based on Fisher's exact test.

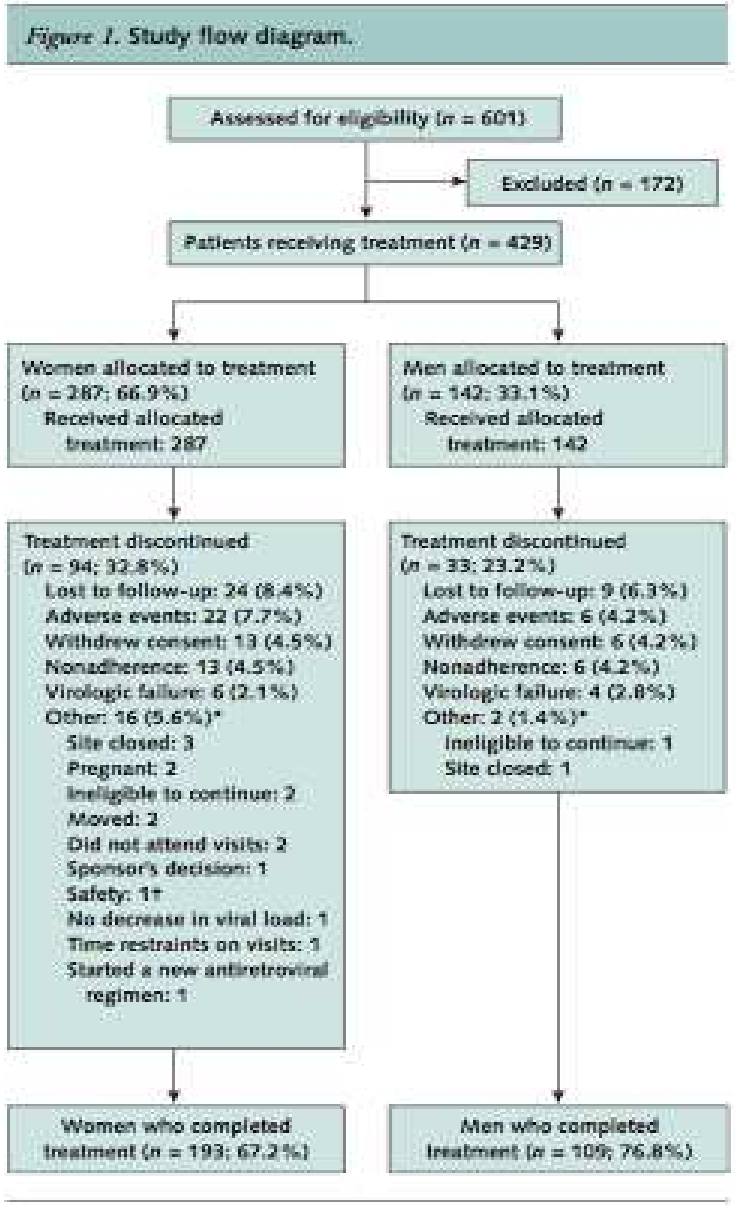
ACTG 5202: Sex and Race Differences in Efficacy and Safety of Initial ART

- **In females, but not males, higher HR for VF with ATV/RTV vs EFV**
  - **ABC/3TC arms: 2.90 (95% CI: 1.32-6.36; *P* = .004)**
  - **TDF/FTC arms: 2.20 (95% CI: 0.97-4.98; *P* = .03)**
- **Females receiving ATV/RTV had higher risk of VF vs males, regardless of NRTIs used**
- **No difference in baseline CD4+ count for females vs males**



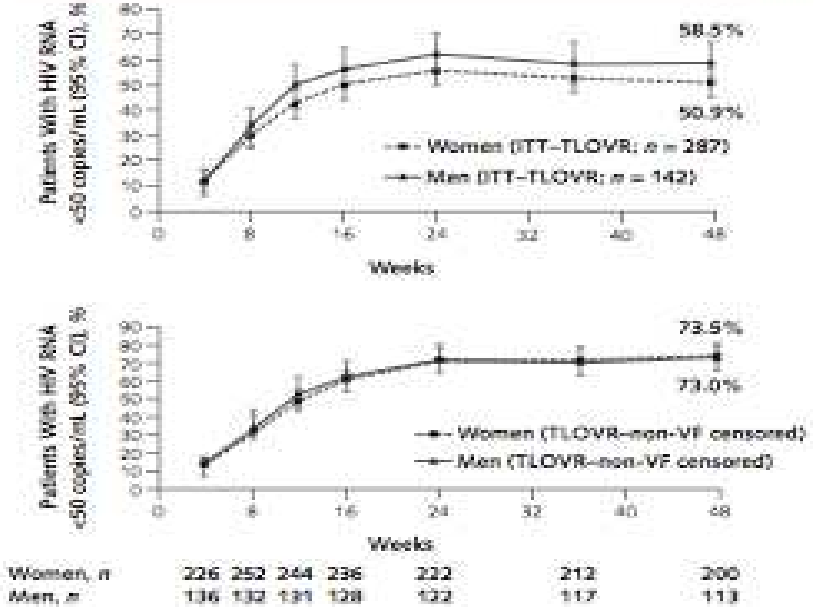
Smith KY, et al. CROI 2011. Abstract 536.

FIG. 2. The GRACE logo for unique branding over the course of the study.



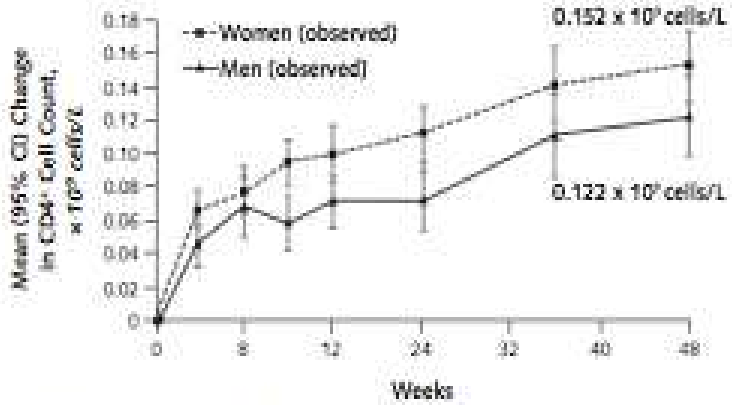
GRACE EFFICACY

Figure 2. Confirmed virologic response in ITT population (*top*) and population that censored patients who withdrew for reasons other than virologic failure (*bottom*).



Women, *n*	226	252	244	236	232	212	200
Men, *n*	136	132	131	128	122	117	113

Figure 3. Mean (95% CI) change from baseline over time in $CD4^+$ cell count (observed).



Women, *n*	255	243	239	234	215	206	188
Men, *n*	133	128	125	125	120	113	105

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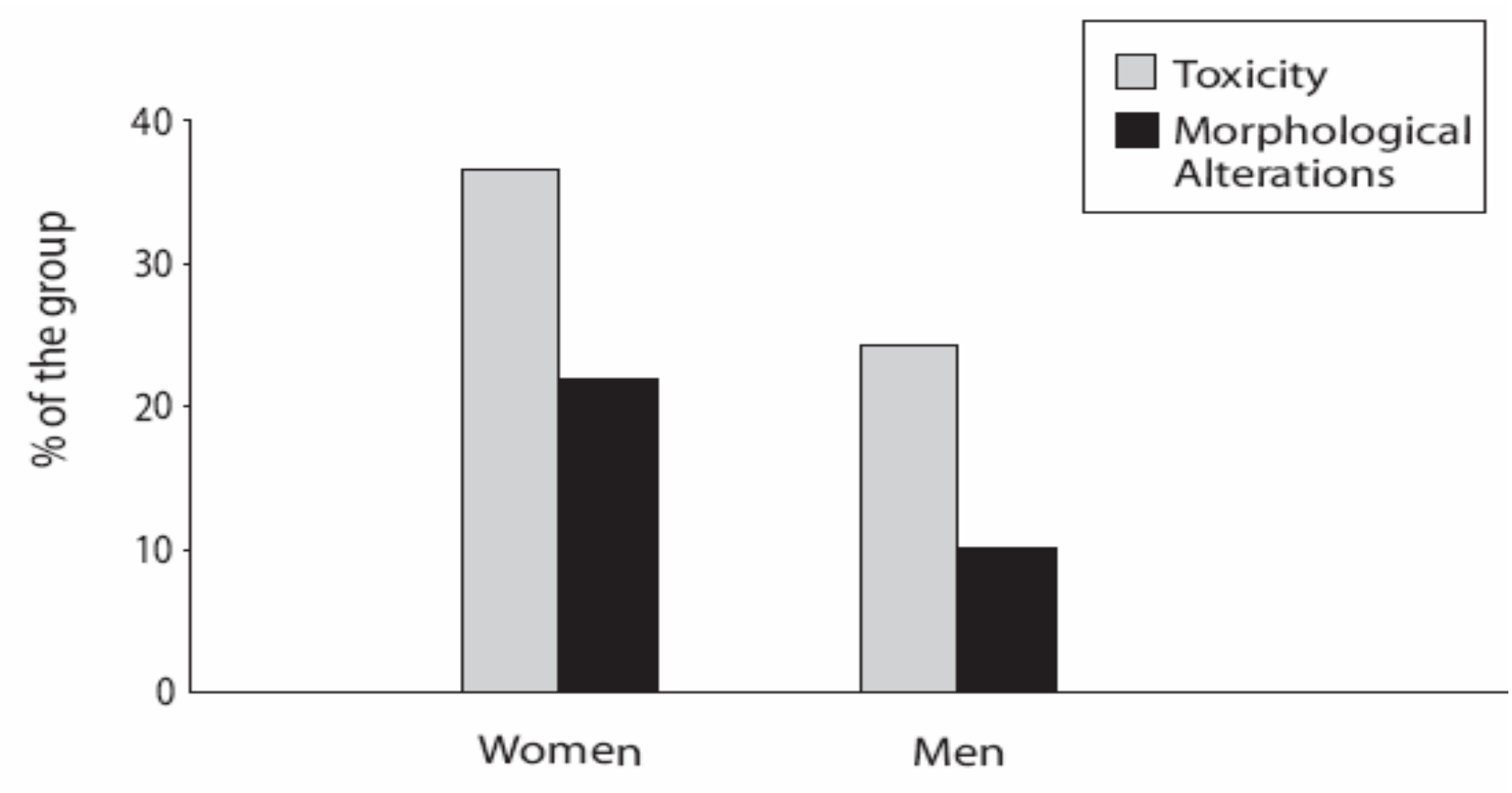
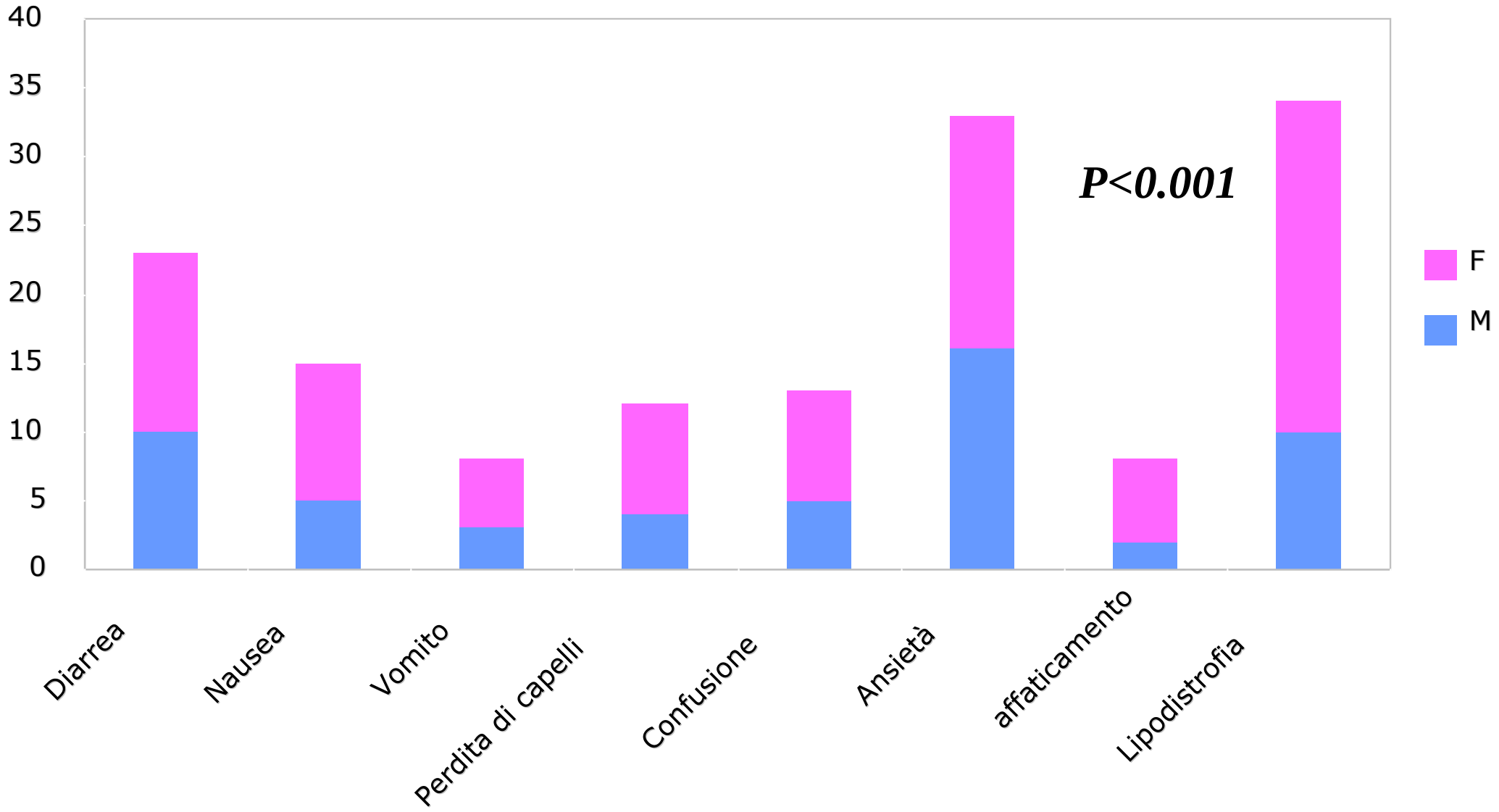
Prevalenza di effetti collaterali HAART-correlati: differenze di genere



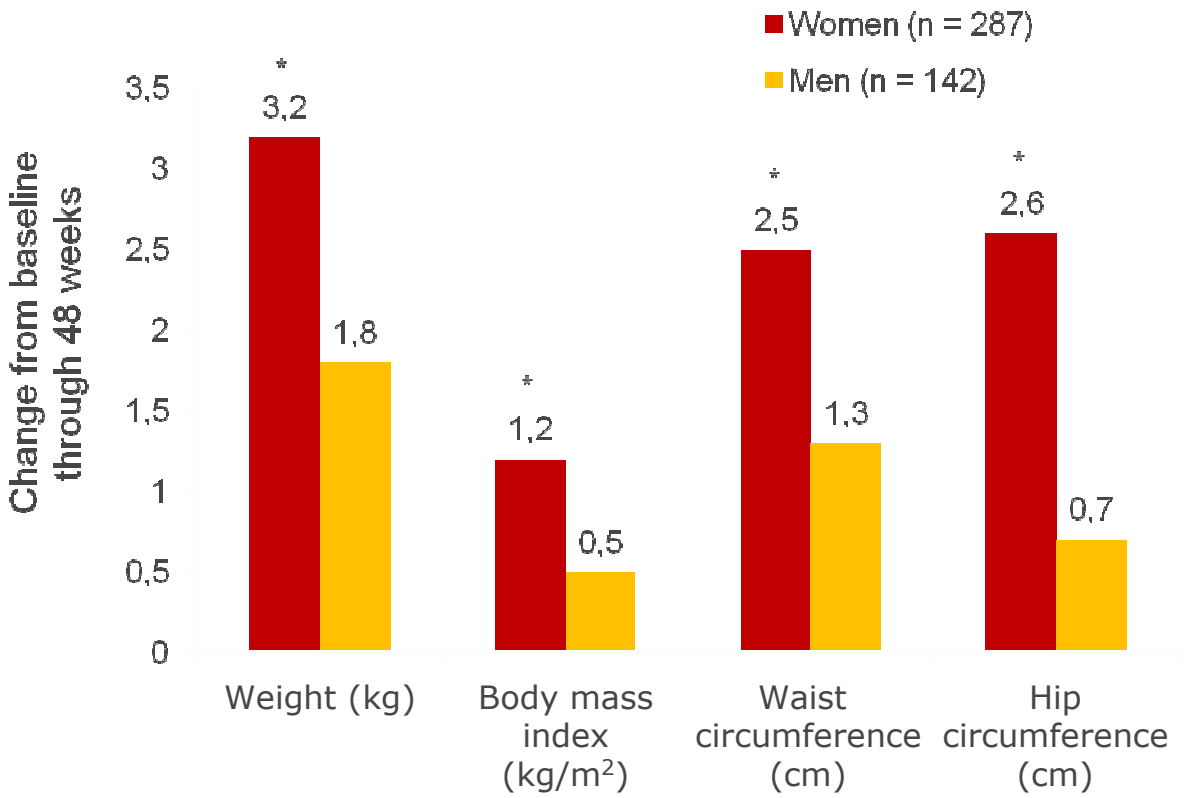
Adapted by Burbano et al. HIV AIDS Rev 2004

Effetti collaterali percepiti dalle pazienti



GRACE study: Metabolic and anthropometric differences between the sexes

- In the GRACE study (darunavir/r BID over 48 weeks), median changes in triglycerides from baseline to Week 48 were greater in men than in women
- Anthropometric parameters increased for both genders over 48 weeks, but larger increases were observed for women than for men
- At Week 48, more women than men reported that their belt or waist size had increased



*p < 0.05 change from baseline to Week 48; GRACE = **G**ender, **R**ace, **A**nd **C**linical **E**xperience; /r = ritonavir

Currier et al. AIDS Patient Care and STDs 2011;25:333–9.

Lipodistrofia nella donna HIV-positiva

- Women generally have a higher percentage of body fat (20-25%) than men (10-15%) and, in general, a lower body weight
- Women store more fat in the gluteal-femoral region, whereas men store more fat in the visceral (abdominal depot)
- There are differences in the prevalence and clinical forms of lipodystrophy observed in HIV-infected men and women[1,2,3]
- Most studies have compared men and pre-menopausal women
  - Observed differences may be attributable to the importance of sex hormones in controlling the total amount of body fat and peripheral fat content in the lower body[4]

1.Galli M et al. JAIDS 2003;34:58. 2. Jacobson D et al. CID 2005;40:1837. 3. McComsey G et al. CID 2009;48:1323. 4. Wells J et al. Best Pract Res Clin Endocrinol Metab 2007;21:415.

Effetti collaterali e HAART

Parlare con il proprio medico della paura degli effetti collaterali della terapia antiretrovirale

Adeguare la terapia antiretrovirale agli stili di vita

Chiedere il cambiamento della terapia se compaiono effetti collaterali

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Aumento del rischio di infarto miocardico nelle donne HIV+

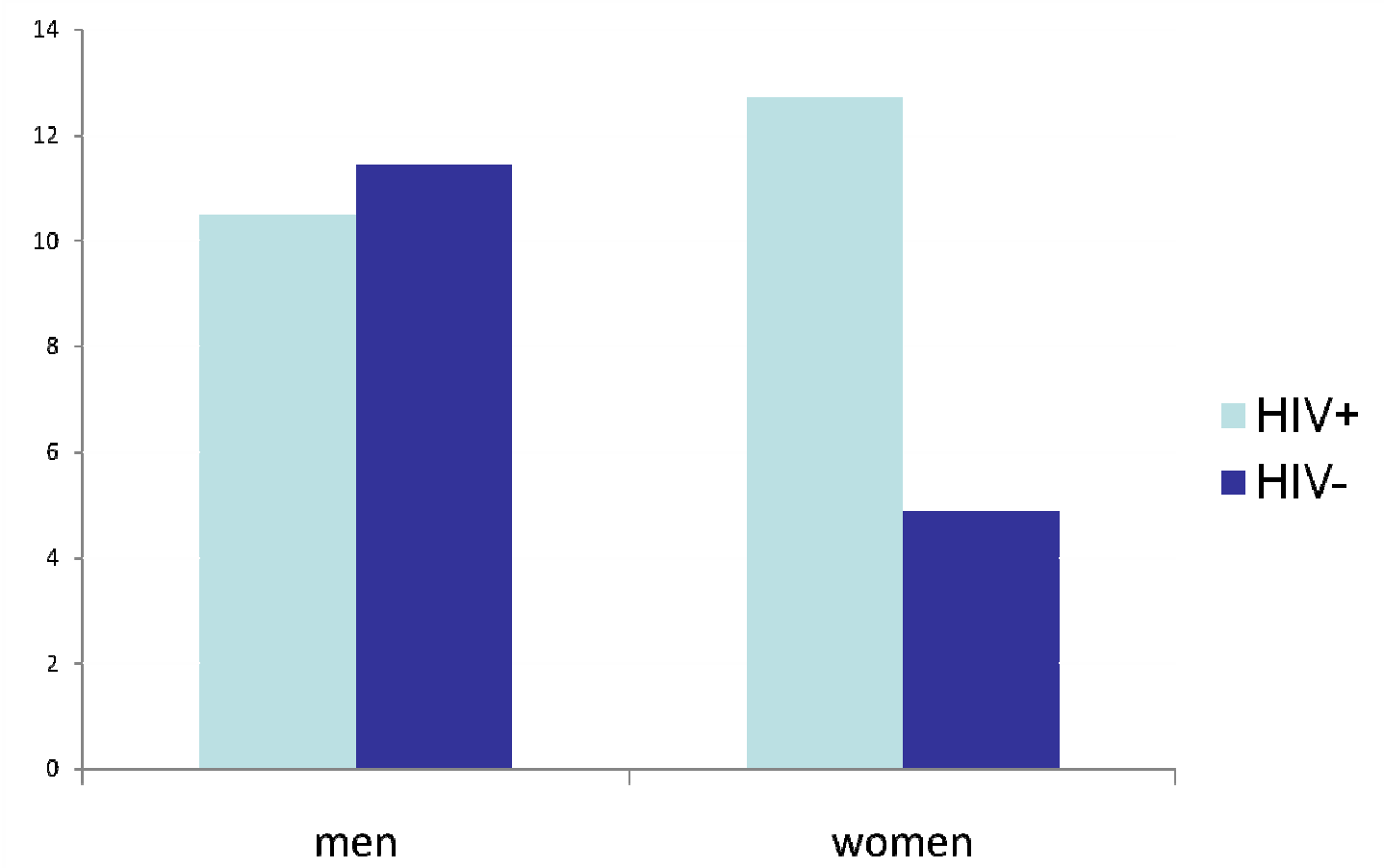
Rischio di IMA: più alto nelle donne rispetto agli uomini

- **2.7 vs 1.4** nella coorte francese
  Lang S. AIDS, 2010

- **3.0 vs 1.4** in French cohort by PRIME model
  Saves M et al. CID, 2003

- **3.0 vs 1.4** nella popolazione USA
  Triant VA et al. J Clin Endocrinol Met, 2007

Increased Acute Myocardial Infarction Rates and Cardiovascular Risk Factors among Patients with Human Immunodeficiency Virus Disease



The RRs for HIV vs non-HIV were 2.98 (p<0.0001) for women and 1.4 for men (p<0.0003)

Triant, et al. The journal of Clinical Endocrinology & Metabolism, 2007

Patologia renale: WISH study

Women's Interagency HIV Study (WISH) is a longitudinal study of the clinical course of HIV infection

- Subjects are followed biannually with a detailed exam including urine analysis, serum creatinine, CD4 cell count, HIV-RNA levels
- 7 years follow-up (1995-2002); 2059 HIV-infected women enrolled

- Proteinuria was defined as > or =+1 on urine dipstick exam on at least two consecutive or nonconsecutive urine analyses, and renal failure was defined as a doubling of serum creatinine
- Proteinuria on initial evaluation: 32%

- Compared with women without proteinuria, women with proteinuria were more likely to be older, black, and to have diabetes, hypertension, a lower CD4 cell count, a higher HIV-RNA level, a lower albumin level and a lower hematocrit
- Proteinuria and an elevated creatinine level are independently associated with a greater risk of progression in AIDS and death

Szczech LA et al, *Kidney Int* 2002

Renal dysfunction among HIV patients starting ARV

RESULTS: Only 129 (36%) of 355 enrolled patients had normal eGFRs (grade 0 or 1) above 90 ml/min per 1.73 m. Grade 2 renal dysfunction (eGFR between 60 and 89 ml/min per 1.73 m) was present in 137 patients (38.6%), and 87 patients (25%) had grade 3 dysfunction (eGFR between 30 and 59 ml/min per 1.73 m). Microalbuminuria and proteinuria were detected in 72 and 36% of patients, respectively. Factors predictive of renal dysfunction in multivariate analysis included female sex [odds ratio (OR) 3.0, 95% confidence interval (1.8-5.1), P < 0.0001], BMI less than 18.5 [OR 2.3 (1.3-4.1), P = 0.004], CD4 T-cell count below 200 cells/μl [OR 2.3 (1.1-4.8), P = 0.04], and WHO clinical stage II or above [OR 1.6 (1.2-2.3), P = 0.001].

	Univariate analysis			Multivariate analysis		
Variable	OR	95% CI	*P* value	OR	95% CI	*P* value
Female sex	3.0	1.8–5.2	0.0001	3.0	1.8–5.1	<0.001
BMI <18.5	2.4	1.4–4.2	0.001	2.3	1.3–4.1	0.004
$CD4^+$ cell count <200	0.47	0.22–0.99	0.046	2.3	1.1–4.8	0.04
WHO clinical stage (II–IV)	5.2	0.94–13	0.001	1.6	1.2–2.3	0.001

CI, confidence interval; OR, odds ratio.

CONCLUSION: Renal dysfunction was highly prevalent in this population of HIV-positive outpatients initiating first ART in Tanzania. This highlights the critical and underappreciated need to monitor renal function in HIV-positive patients in sub-Saharan Africa, particularly given the increasing use of tenofovir in first-line ART.

Msango L. *AIDS* 2011.

Osteopenia e Osteoporosi

- In 31 donne HIV+ in menopausa (ispaniche e afro-americane) *vs* 186 controlli:

  - Osteoporosi era presente in :

  42% in HIV+ vs 23% in HIV- a livello lombare (p=0.03)

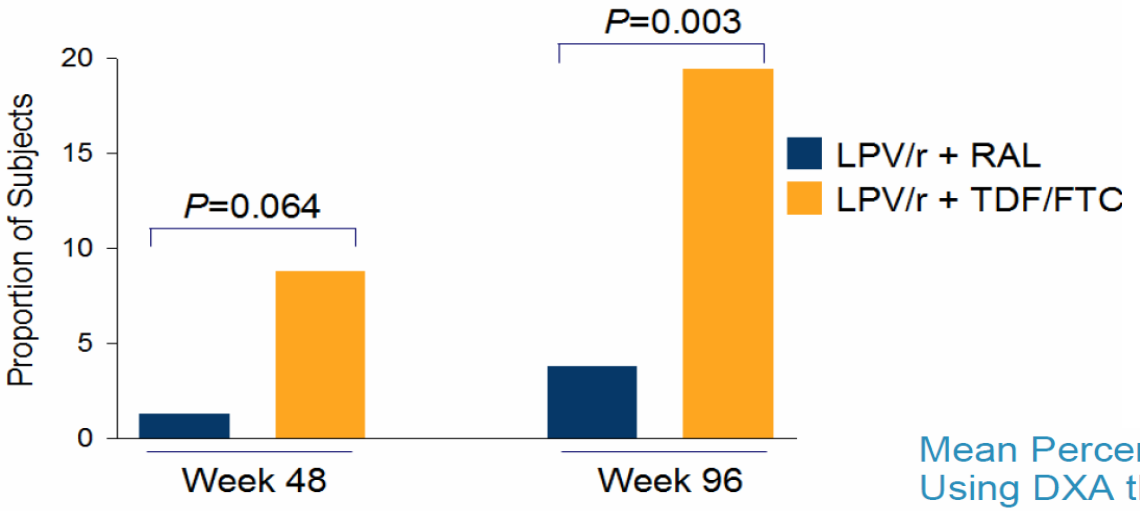
  10% in HIV + vs 1% in HIV – a livello femorale (p=0.03)

  - Fattori correlati ad alterazione del BMD risultavano basso BMI, ridotto peso corporeo e tempo di comparsa di menopausa

Yin et al. Osteoporos 2005

Bone Mineral Density (BMD) Analysis in ART-Naïve Subjects Taking LPV/r Combined with RAL or TDF/FTC for 96 weeks in the PROGRESS Study

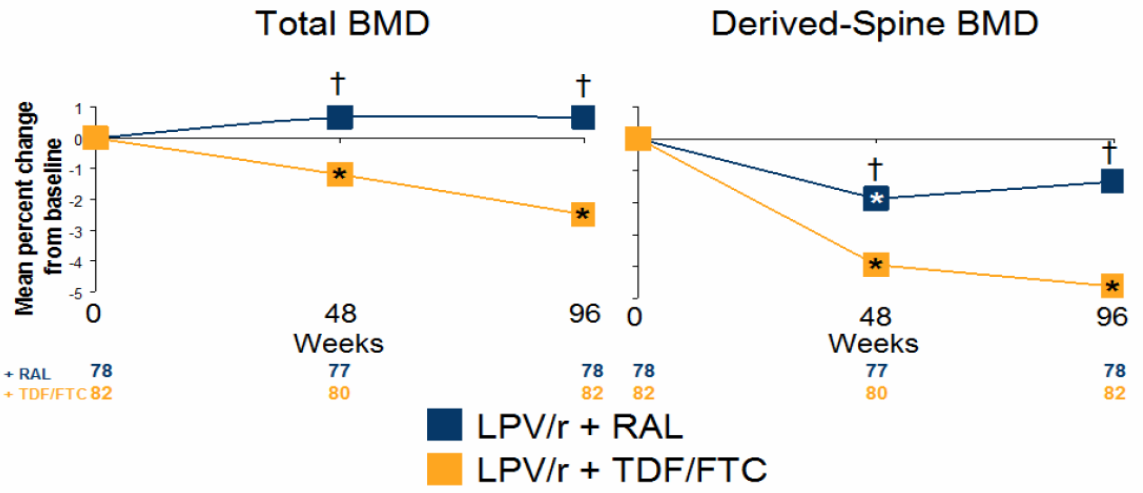
Proportion of Subjects with ≥5% Decrease from Baseline in Total Bone Mineral Density



N		
LPV/r + RAL	77	78
LPV/r + TDF/FTC	80	82

P-values calculat

Mean Percent Changes in Bone Mineral Density Analyzed Using DXA through 96 Weeks of Treatment



N					
LPV/r + RAL	78	77	78	78	77	78
LPV/r + TDF/FTC	82	80	82	82	80	82

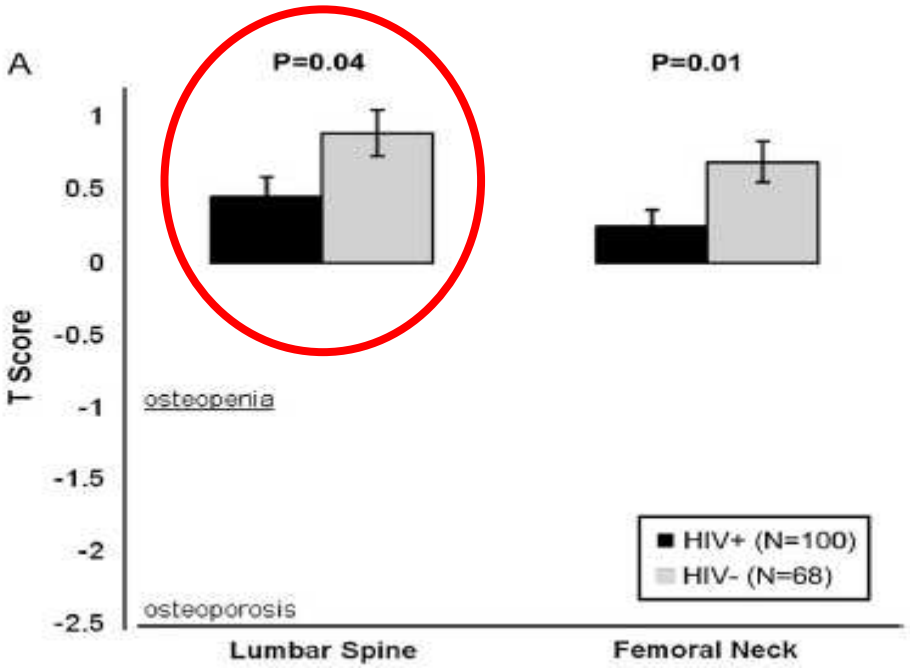
*Within group P-value <0.05
†Between group P-value <0.05

P-values calculated using One-way ANOVA

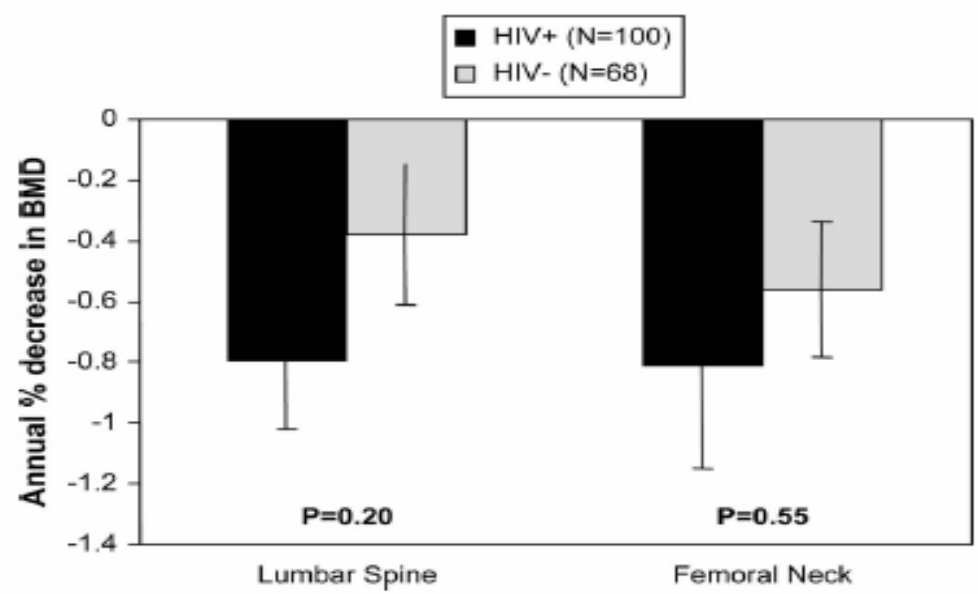
Qaquish et al.
3th International Workshop on Adverse Drug Reactions and Co-Morbidities in HIV
14-16 July 2011—Rome, Italy

Short-term bone loss in HIV-infected premenopausal women

BMD at index visit



Annual percent decrease in BMD



Yin et al, *JAIDS* 2010; 53: 202-208

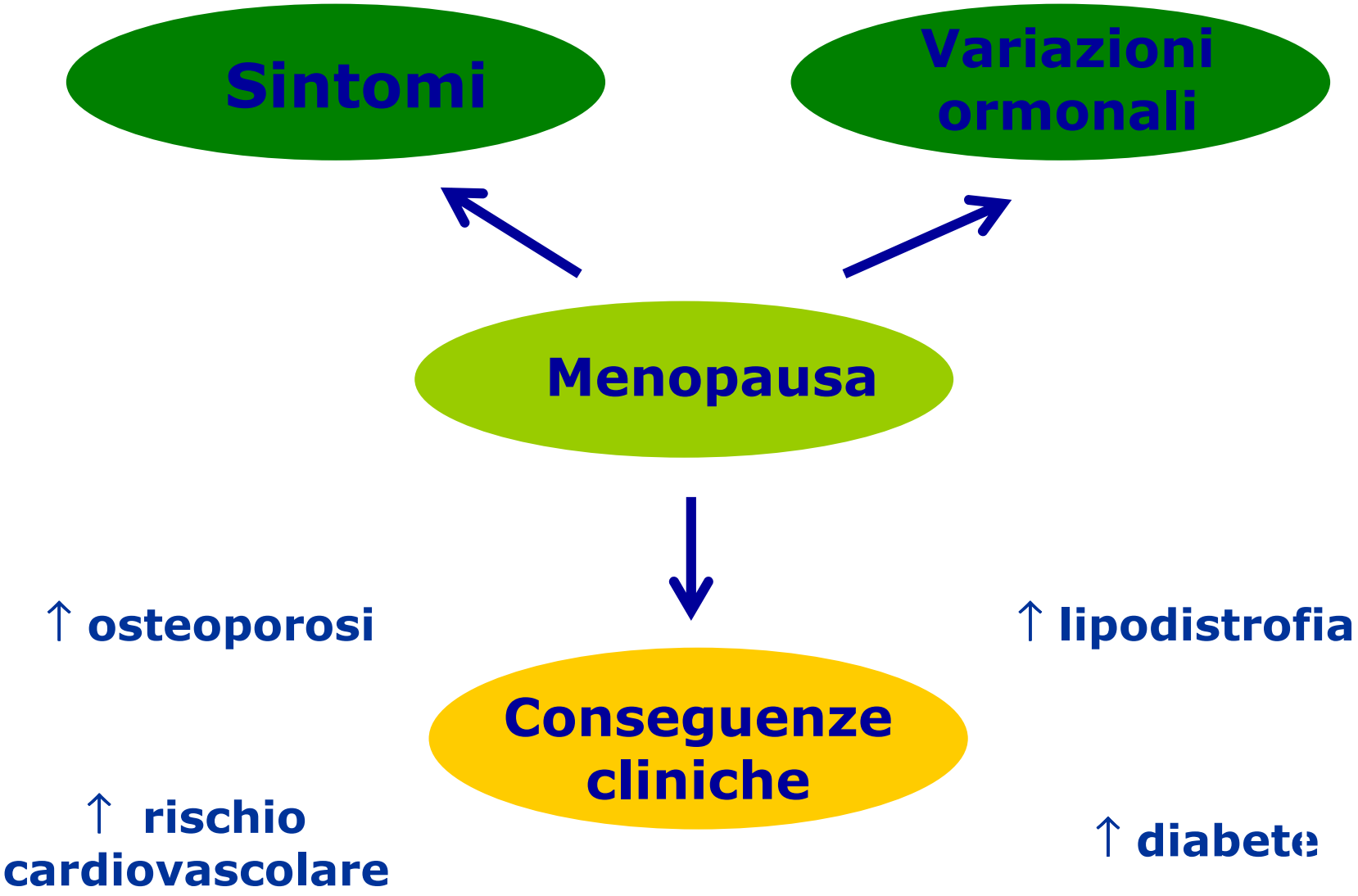
Esecuzione di screening metabolici

- Valutazione screening cardiovascolari
- Valutazione tossicità ossea
- Valutazione tossicità renale
- Visita ginecologica con PAP-test e ricerca HPV

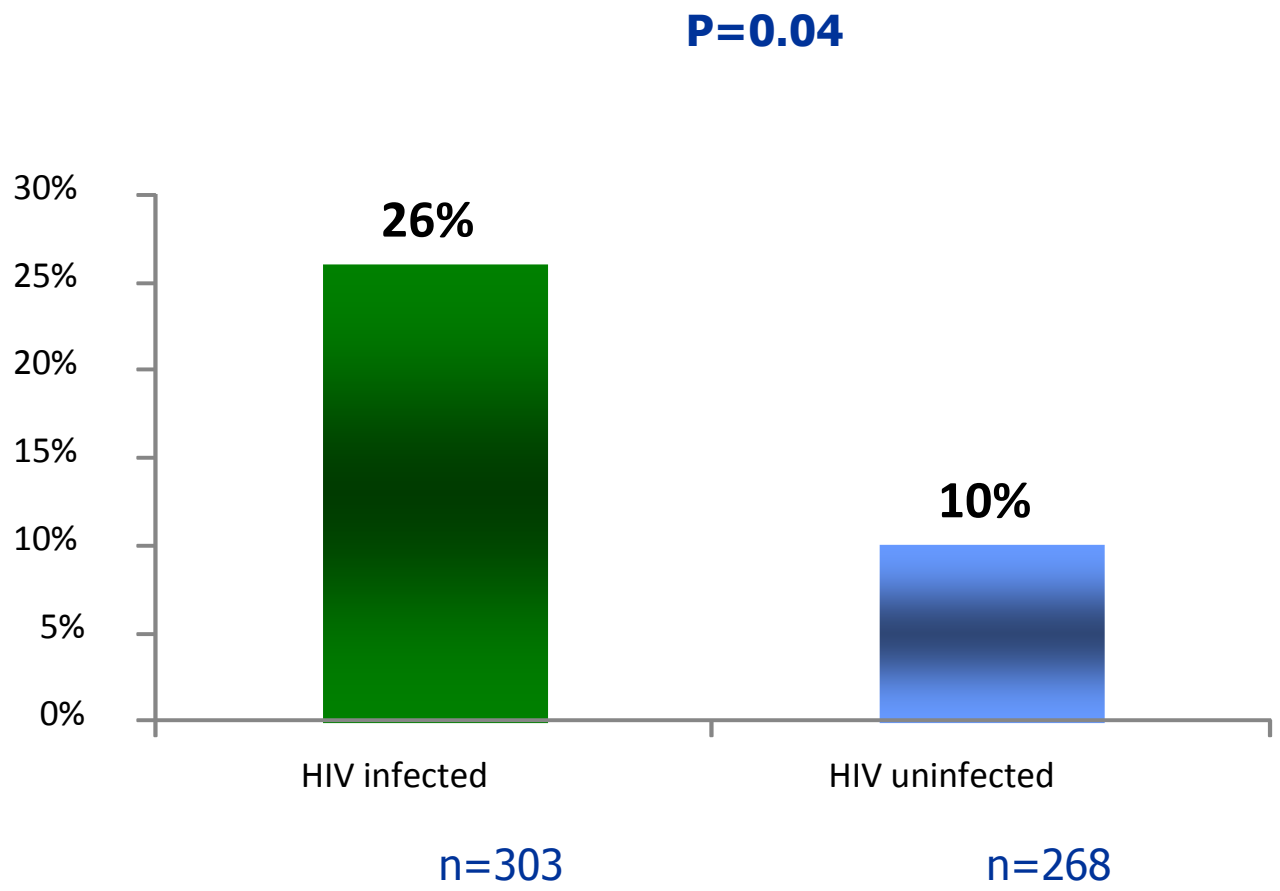
Come posso ridurre il rischio?

- Modifica stili di vita
- Astensione dal fumo
- Sana alimentazione
- Esercizio Fisico

La menopausa nelle donne HIV +



Menopausa in età precoce (< 40 aa)



Women living with HIV were 73% more likely to experience early onset of menopause, compared with HIV-uninfected women (P=0.024) (46 *vs* 47)

Schoenbaum et al . Clin Infect Dis 2005.

CORRELATES OF EARLY MENOPAUSE IN HIV-INFECTED WOMEN (DIDI STUDY)

- Italian multicenter study based on an anonymous questionnaire surveillance performed by 585 HIV positive women during year 2010 followed at 16 Clinic of Infectious Diseases.
- Inclusion criteria: women aged 18 years or older, with a good understanding of Italian language
- Items covered from the questionnaire: women socio-demographic characteristics, data on recreational drug use and smoking, spiritual and religious attitude, sexual and gynecological health,

WOMEN FOR POSITIVE ACTION

DIDI study
dedicato a Raffaella Rosso

How was your menstrual flow in the last 12 months?

- As usual
- Frequency increased
- Frequancy decreased
- Intensity increased
- Intensity decreased
- Absent

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Conclusions

- The prevalence of menopause at age <=45 (7.7%) was comparable with the one reported in the Italian general population (7.1%), however we observed higher proportion of menopause in women <=40 years old (5.2% vs. 1.8%)
- Advanced stage of disease represents the main predictor of menopause at age <=45
- As suggested by good clinical practice, post-menopausal HIV italian women more likely undergo annual co-morbidity

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HIV e differenze di genere: possibili discriminanti

- Modalità di infezione
- Accesso alle cure
- Aderenza alla terapia
- Progressione di malattia/outcome del trattamento
- Tossicità/interazioni farmacologiche
- Comorbidità/morbidità legata all'invecchiamento
- Maternità