Le nuove sfide dell'HIV

Caso clinico

"Un paziente altoviremico"

Giuseppina Liuzzi

Istituto Nazionale per le Malattie Infettive

"Lazzaro Spallanzani"

Caso clinico(1)

In data 29.10.15

- Donna in gravidanza 19a sett
- Sifilide latente (VDRL: neg TPHA: pos), test HIV negativo
- Viene richiesta al partner sierologia per sifilide e test HIV

- Partner D.M. 45 aa
- 2006 ricovero per Epatite B acuta (test HIV negativo)
- Frequenti episodi di herpes genitale, herpes zoster, leucopenia, numerose visite mediche MAI RICHIESTO TEST HIV

In data 04.11.2015 test HIV: positivo

In data 12.11.2015 HIV-RNA:1.133.504 cp

CD4: 392/mmc HLAB 570: assente

ISTITUTO NAZIONALE PER LO STUDIO DELLE MALATTIE INFETTIVE
IRCCS "LAZZARO SPALLANZANI"

Unità Monitoraggio
Terapie Antiretrovirali
Dirigente Medico Responsabile Prof. Carlo-Federico Perno
Tel. 06 55170654/656 – Fax. 06 5594555

GENOTIPIZZAZIONE
MODULO DI RISPOSTA

NOME PAZIENTE: [redacted]

UNITA' OPERATIVA — MEDICO CURANTE: DOTT.SSA PITTALIS

DATA PRELIEVO: 12-11-15 — DATA REFERTO: 27-11-15

MUTAZIONI NOTE:

PROTEASI: L10I/V, M36I, L63S

TRASCRITTASI INVERSA: E138A

ALTRE MUTAZIONI:

PROTEASI: I13V, I15V, L19I, N37T, R41K, R57K, Q61N, E65D, H69Q

TRASCRITTASI INVERSA: V35T, T39L, V60I, D86E, I135L, I142T, E169D, D250E, A272P, K277R, T286P, P294S, E297K, Q334Y

RISULTATO

PR: Presenza di mutazioni secondarie
RT: Presenza di una mutazione

FARMACI POTENZIALMENTE EFFICACI:

PR: Tutti con boost di Ritonavir
RT: Tutti (vedi interpretazione)

NOTE: L'analisi filogenetica della sequenza nucleotidica del gene pol indica la presenza di sottotipo virale CRF12_BF.

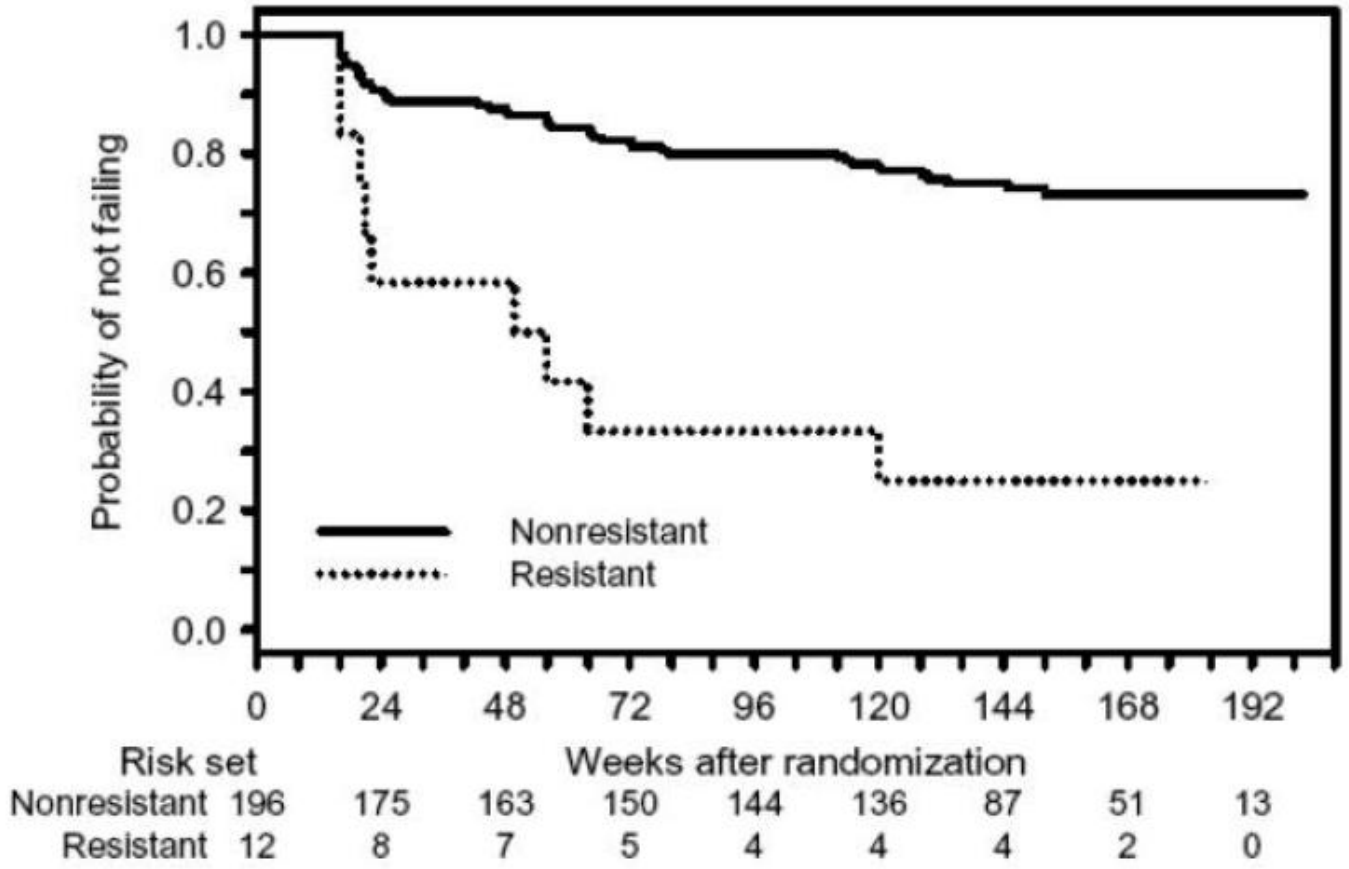
INTERPRETAZIONE VIROLOGICA: Quadro genotipico wild type.
Si segnala la presenza di una mutazione polimorfa E138A, di non chiara interpretazione clinica, ma potenzialmente associabile ad un aumentato rischio di resistenza a NNRTI, soprattutto di II generazione. Utile pertanto considerare tali farmaci solo nel contesto di un'elevata aderenza, anche alla luce della viremia molto elevata.

Il Responsabile

Via Portuense, 292 – 00149 Roma – tel. 06 551701- C.F e P.IVA 05080991002

Quadro genotipico di wild type.
Presenza di una mutazione polimorfa E138A
Potenzialmente associabile ad un aumentato rischio di resistenza a NNRTI , soprattutto di II generazione

The presence of transmitted drug resistance detected by standard resistance testing correlates with a shorter time to first virologic failure



Weighted Cox proportional hazard models including baseline NNRTI resistance showed a significantly increased risk of virologic failure for subjects with NNRTI-resistant virus at baseline compared with those without (intent-to-treat: HR, 2.27 [95% CI, 1.15–4.49]; *P .018) (as-treated: HR, 2.61 [95%* CI, 1.30 –5.20]; *P .007)*

Kuritzkes et al ● **JID 2008:197**

Public health importance of individuals with high viral load

- Increased HIV infectiousness
- Faster progression to AIDS
- Single, high viral load
  - Can be used as an indicator
- Sustained high viral load reflect
  - Lack of adherence to ART
  - Sporadic access to care and treatment
  - Infection with ART-resistant strain
  - In care but not on ART
  - Terminal stage of HIV infection

Impact of baseline viral Load and Time to Viral Suppression on Virologic Rebound according to first-line ART
SPEED Study

Lydie Khatchatourian, Matthieu Hanf, Thomas Jovelin, Nolwenn Hall, Véronique Joly, Eric Cua, Pierre Delobel, Tristan Ferry, Christine Katlama, Antoine Cheret, François Raffi, Clotilde Allavena, and Dat'AIDS Study Group

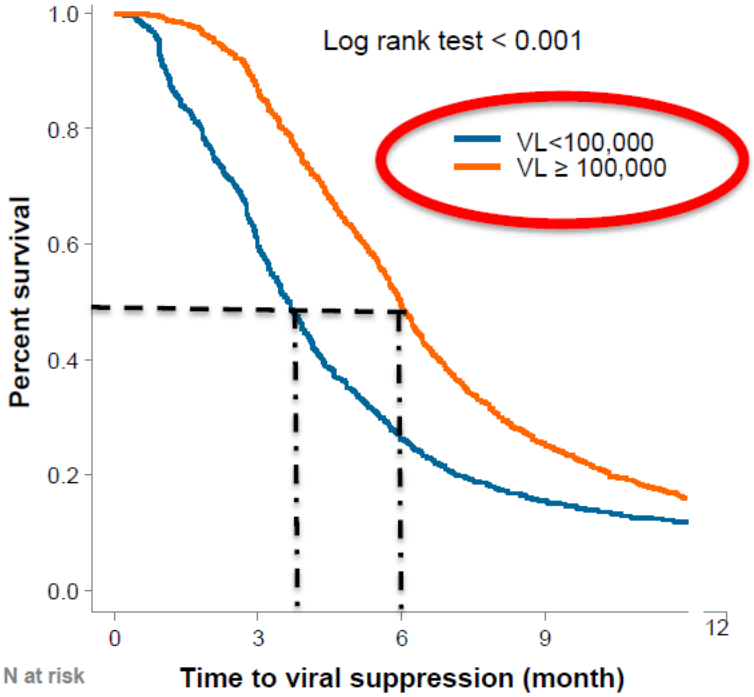
Khatchatourian L. et al. EACS 2015, Abs. PS 10/1

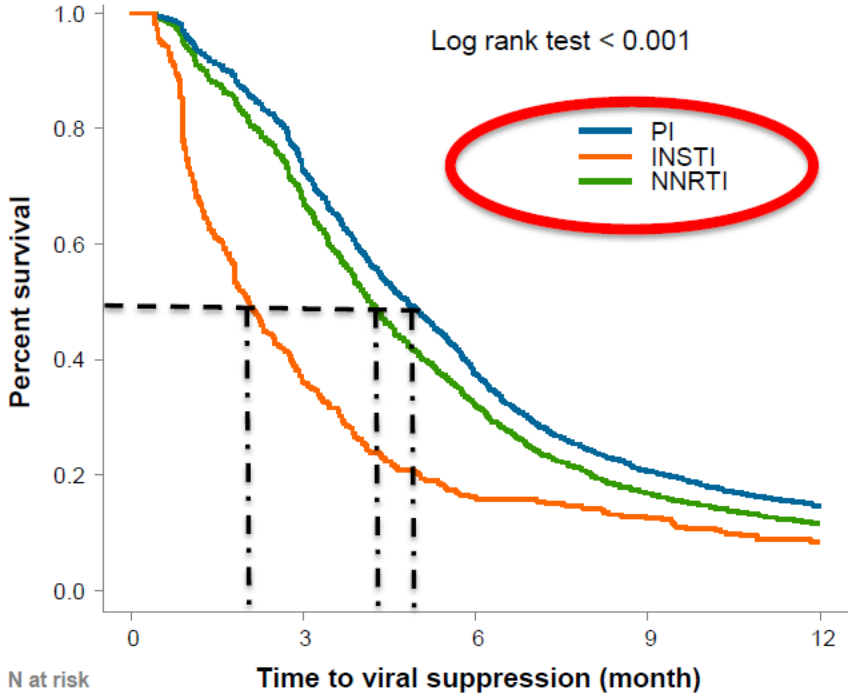
Time to observed viral suppression according to baseline VL and to regimen class

Time to viral suppression according to baseline VL

Time to viral suppression according to regimen class

N=8351





N at risk

VL < 100,000	5135	2959	1280	730	530
VL ≥ 100,000	3216	2664	1477	732	442

N at risk

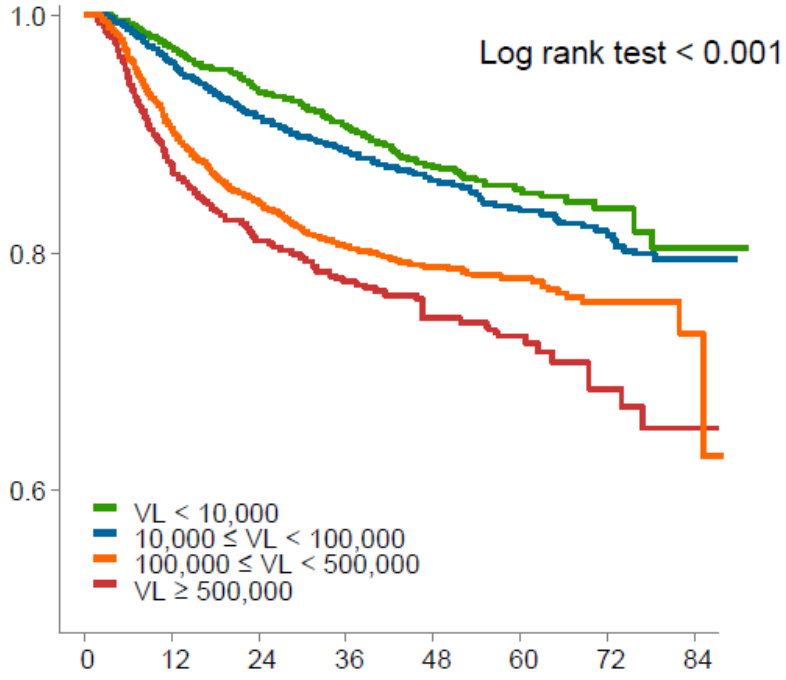
PI	5828	4088	2049	1086	729
INSTI	377	131	57	42	26
NNRTI	2146	1404	651	334	217

Risk of virologic rebound according to baseline viral load and time to viral suppression

- 990 (13.0%) patients experienced virologic rebound (CV > 50 copies/ml X2)
  - Median [IQR] follow-up time from cART initiation : 41.2 [23.8,61.5] months

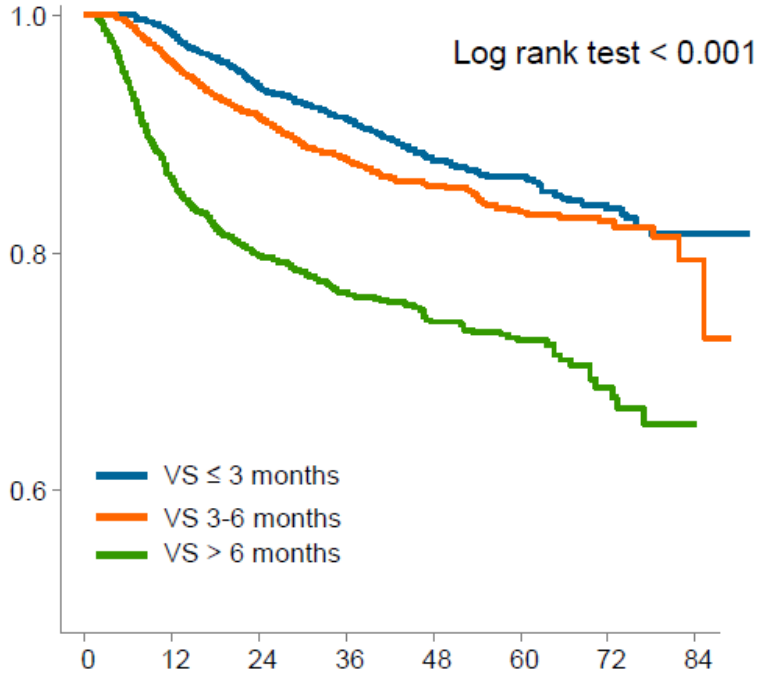
N=7592

Time to virologic rebound according to baseline viral load



N at risk								
VL < 10,000	1556	1283	996	715	503	302	131	34
10,000-100,000	3189	2562	1931	1362	873	519	241	46
100,000-500,000	2036	1514	1125	784	516	315	132	12
VL > 500,000	8141	555	390	292	189	110	55	2

Time to virologic rebound according to time to viral suppression



N at risk								
VS ≤ 3 months	2454	2096	1663	1227	841	547	274	70
VS 3-6 months	2772	2219	1669	1167	780	444	197	24
VS > 6 months	2366	1599	1110	759	460	255	88	

Readiness for Therapy: A Key Decision Point

Linee Guida Italiane sull'utilizzo dei farmaci antiretrovirali
e sulla gestione diagnostico-clinica
delle persone con infezione da HIV-1

17 Dicembre 2015

In collaborazione con:

Ministero della Salute
Sezioni L ed M del Comitato Tecnico Sanitario

SIMIT
Società Italiana di Malattie Infettive e Tropicali

Tabella 2a - Regimi raccomandati per l'inizio della cART.

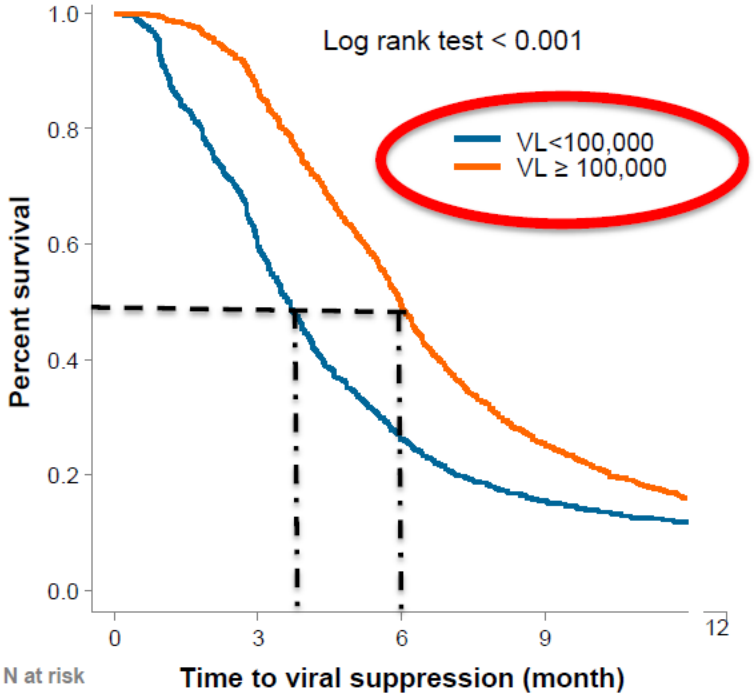
REGIME	RACCOMANDAZIONE (FORZA/EVIDENZA)	RIFERIMENTI BIBLIOGRAFICI
Regimi raccomandati		
TDF/FTC+RAL	[AI]	[23-24,26,31-32]
TDF/FTC/EVG/COBI	[AI]	[27-30,66]
TAF/FTC/EVG/COBI	[AI]	[72]
TDF/FTC+DTG	[AI]	[31-32,34]
ABC/3TC+DTG	[AI]	[31-34]
ABC/3TC/DTG	[AI]	[31-35]
TDF/FTC/RPV (in caso di valori di HIV-RNA < 100.000 cp/mL e conta di T CD4+ > 200 cellule/µL)	[AI]	[12,14,18,19]

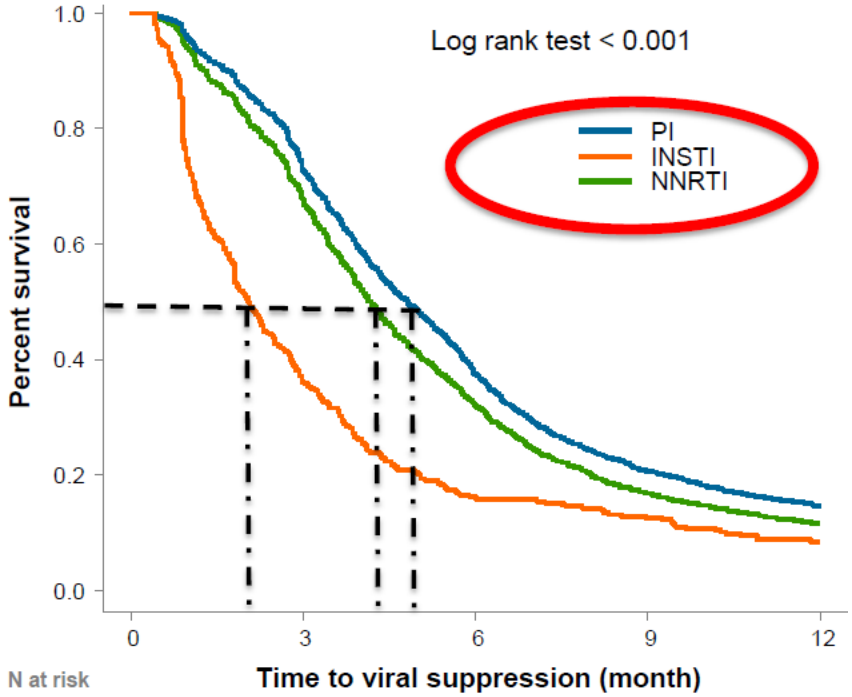
Time to observed viral suppression according to baseline VL and to regimen class

Time to viral suppression according to baseline VL

Time to viral suppression according to regimen class

N=8351





N at risk

VL < 100,000	5135	2959	1280	730	530
VL ≥ 100,000	3216	2664	1477	732	442

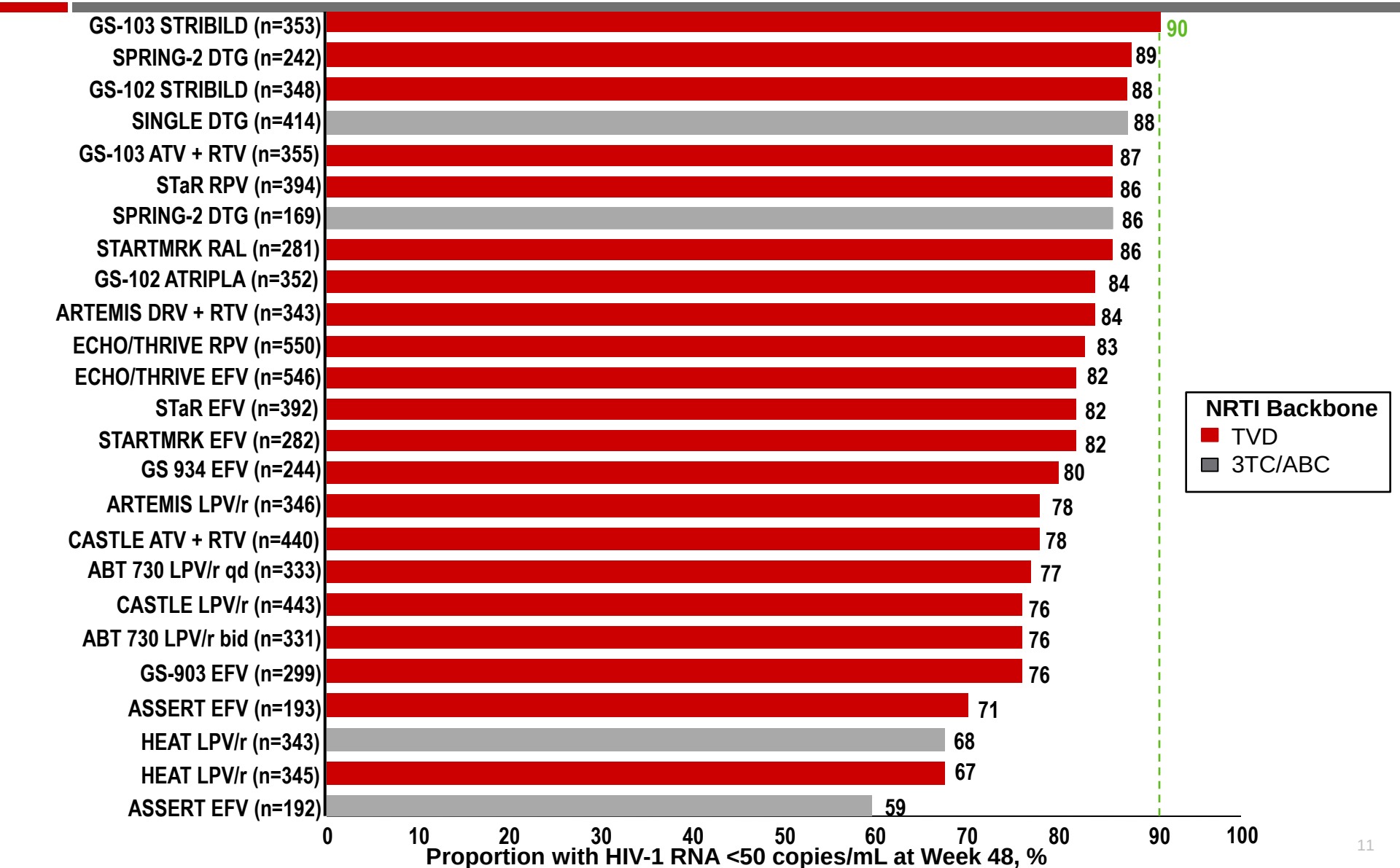
N at risk

PI	5828	4088	2049	1086	729
INSTI	377	131	57	42	26
NNRTI	2146	1404	651	334	217

Registrational Treatment-Naive Clinical Trials: Historical Data*

HIV RNA <50 c/mL at Week 48

This slide depicts data from multiple studies published from 2004-2014. Not all regimens have been compared head-to-head in a clinical trial



Which Patient for TDF/FTC/EVG/COBI?

Considerations in Favor

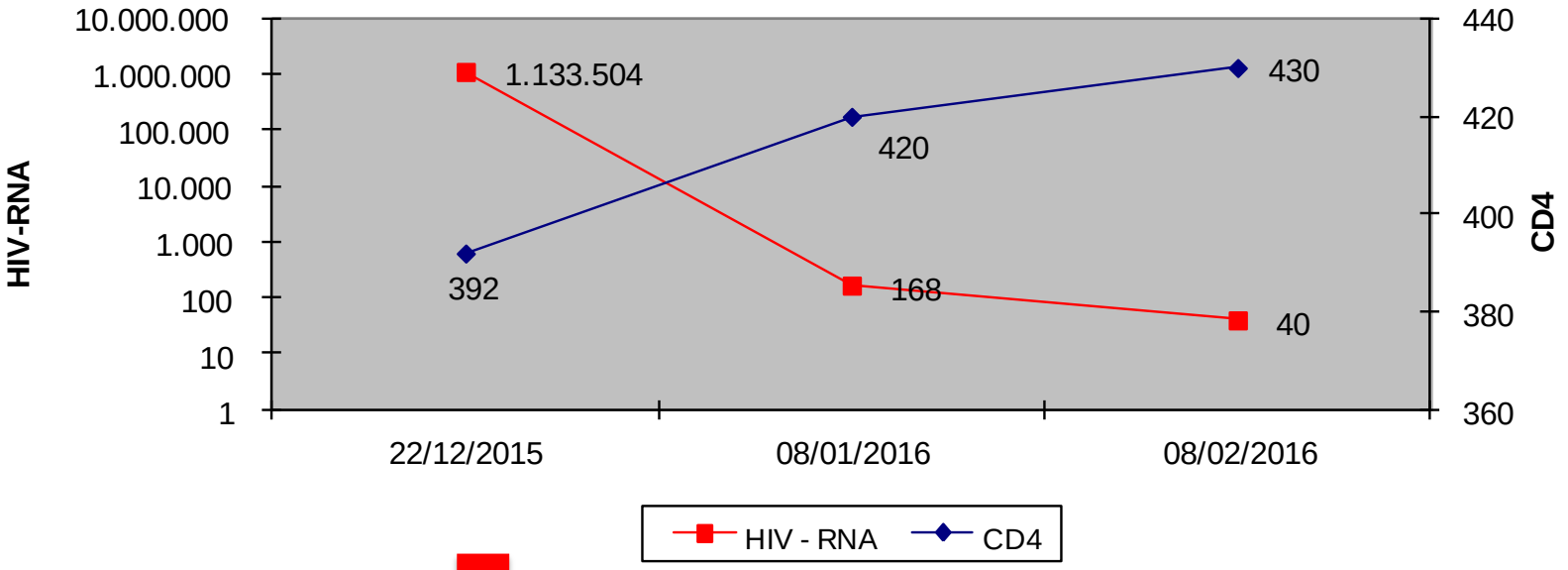
- Coformulated/1 pill dally
- Once-daily INSTI regimen
- Noninferior to EFV and ATV/RTV across HIV-1 RNA, CD4+ strata[1,2]
- Fewer CNS AEs than EFV[1]

Considerations Against

- Includes pharmacologic booster
- High risk of resistance at VF[1-4]
- Cross resistance with RAL[5]
- Drug–drug interactions[6]
- Concerns about monitoring renal function with COBI[6]

1. Zolopa A, et al. J Acquir Immune Defic Syndr. 2013;63:96-100. 2. Rockstroh J, et al. J Acquir Immune Defic Syndr. 2013;62:483-486. 3. Sax PE, et al. Lancet. 2012;379:2439-2448. 4. DeJesus E, et al. Lancet. 2012;379:2429-2438. 5. DeJesus E, et al. IAS 2007. Abstract TUPEB032. 6. TDF/FTC/EVG/COBI [package insert].

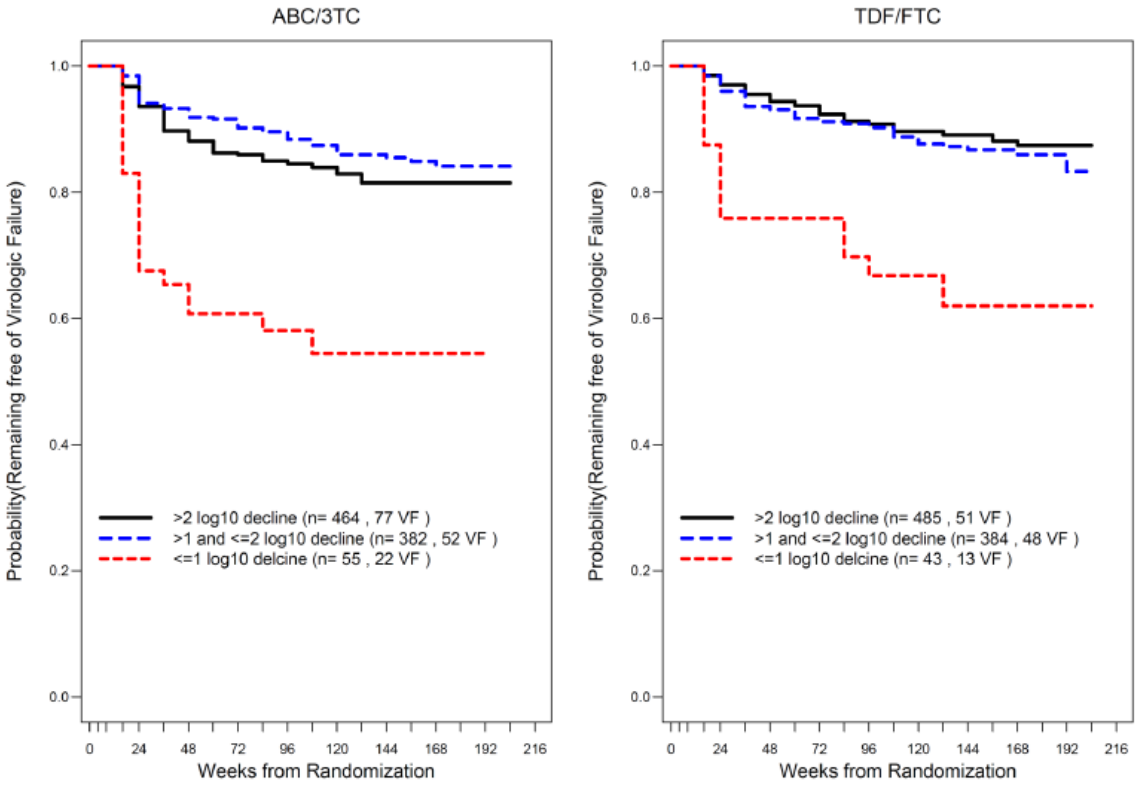
Caso Clinico (1)



Inizia terapia con STRIBILD

A viremia decline of <1log at week 4 is significantly associated with increased risk of virological failure

Figure 3: Time to Virologic Failure by Week 4 Viral Load Change



In landmark analysis, smaller Week 4 VL decline was associated with increased risk of VF.

HR (95% CI) (per 1 $\log_{10}$ copies/mL less decline)

ABC/3TC:
Univariate 1.33 (1.05, 1.69)
*Adjusted 1.90 (1.52, 2.38)

TDF/FTC:
Univariate 1.80 (1.38, 2.34)
*Adjusted 1.79 (1.38, 2.33)

*Adjusted for age, sex, race/ethnicity, history of intravenous drug use, whether genotype was performed pre-enrollment, history of AIDS, hepatitis B or C infection and baseline VL and CD4.

Grant et al., CROI 2011

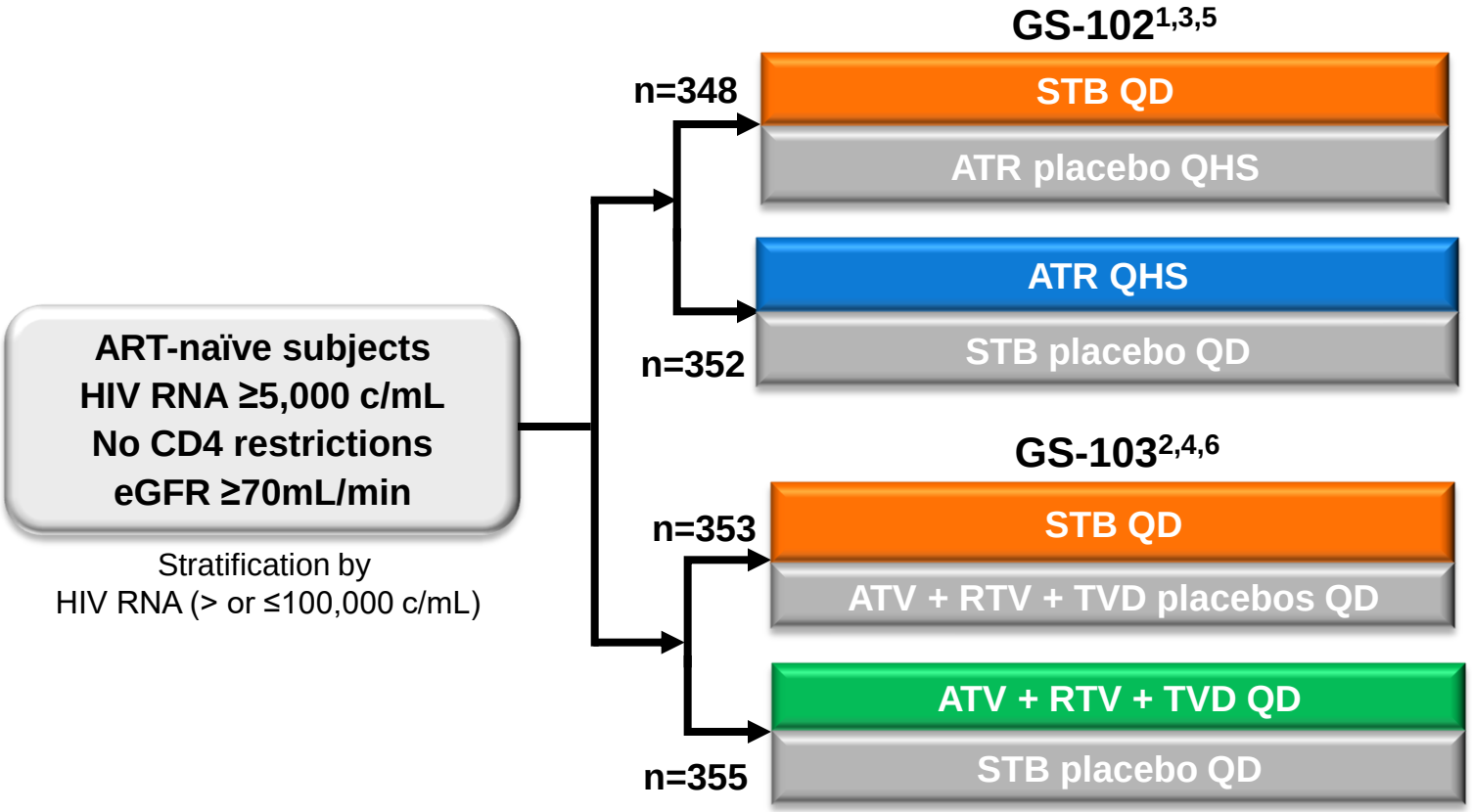
Comparing the Integrase Inhibitors

Agent	Advantages	Disadvantages
Raltegravir	▪ Longest experience ▪ Fewer drug interactions than EVG, DTG	▪ Twice daily dosing (for now) ▪ No coformulation
Elvitegravir	▪ Single-tablet regimen (STR) ▪ Once-daily dosing	▪ Requires COBI boosting ▪ COBI drug interactions similar to RTV
Dolutegravir	▪ The only non-TDF–containing STR ▪ Once-daily dosing ▪ Higher barrier to resistance ▪ Few drug interactions ▪ Active against some RAL- and EVG-resistant virus	▪ Coformulated with ABC/3TC

Together, the results of STARTMRK, GS 102 and 103, SINGLE, FLAMINGO, and ACTG 5257 suggest that integrase inhibitor–based regimens are the preferred starting regimens in the majority of pts

Study Design

Randomized, double-blind, double dummy, active-controlled study



Primary Endpoint: Non-inferiority (12% margin) of STB to comparator arm by FDA snapshot analysis HIV-1 RNA <50 copies/mL at 48[1,2] weeks

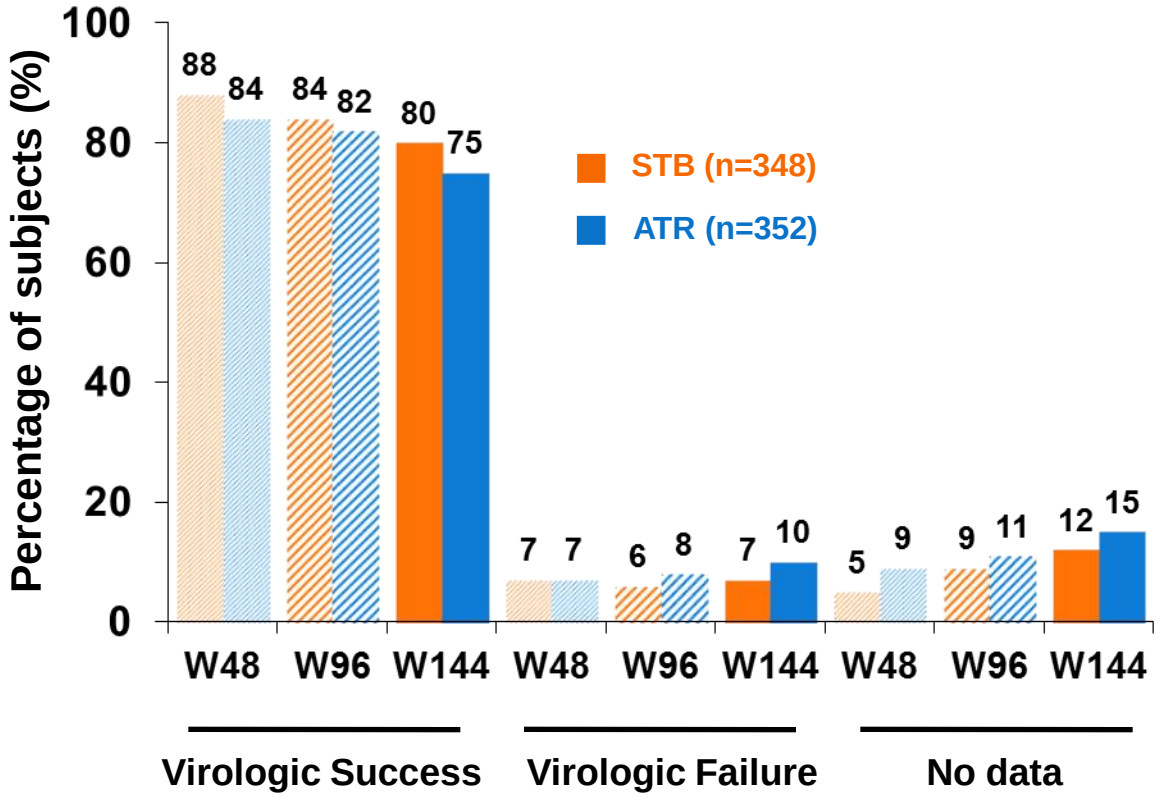
Secondary Endpoints: Efficacy, safety, and tolerability observed through Week 96[3,4] and 144[5,6]

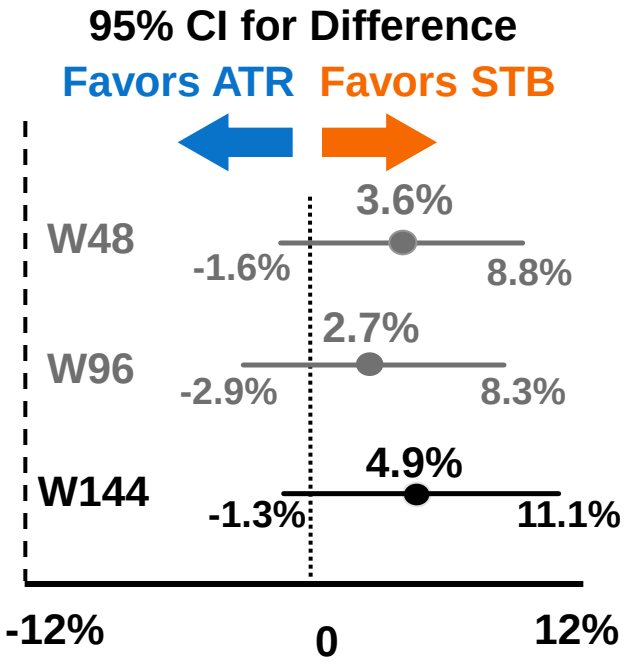
STB = Stribild® = EVG/COBI/TVD; ATR = Atripla® = EFV/TVD; TVD = Truvada® = FTC/TDF

1. Sax P, et al. Lancet 2012; 379:2439-48
2. DeJesus E, et al. Lancet 2012; 379: 2429-38
3. Zolopa A, et al. JAIDS.2013; 63:96-100
4. Rockstroh JK, et al. JAIDS 2013; 62:484-486
5. Wohl D, et al. JAIDS 2014; 65 (3):e119-121
6. Clumeck N, et al. JAIDS 2014; 65 (3):e121-124

Virologic Outcomes

Virologic success (HIV-1 RNA <50 copies/mL) as defined by FDA Snapshot algorithm





Wohl D, et al. JAIDS 2014; 65 (3):e119-121

‡

Efficacy By Backbone And In High Viral Load Patients At Week 48

Baseline Characteristics	SPRING-2[1]	SINGLE[2]	FLAMINGO[3]	Study 102[4]	Study 103[5]
	2 NRTI + DTG 50 mg QD	2 NRTI + + DTG 50 mg QD	2 NRTI + + DTG 50 mg QD	EVG/COBI/ FTC/TDF STR	EVG/COBI/ FTC/TDF STR
Number of patients	411	414	242	348	353
% VL >100,000 copies/mL	28%	32%	25%	34%	42%
VL> 100,000 copies/mL and on TDF/FTC, N	77	N/A	48	118	150
VL> 100,000 copies/mL and on ABC/3TC, N	37	134	13	N/A	N/A

- ARV naïve patients with VL >100,000 copies/mL on ABC/3TC + DTG on the DTG label
  - **SPRING-2, n=37; SINGLE: n = 134; FLAMINGO: n=13 total n=184**
- ARV naïve patients with VL > 100K copies/mL on TDF/FTC on the STRIBILD label
  - **Study 102; n=118; study 103; n=150: total n=268**

This slide reflects data from multiple clinical trials: the regimens have not been compared head-to-head in a clinical trial. No assertions on comparative clinical efficacy are made or inferred.

1. Raffi F, et al. Lancet Infect Dis 2013;381: 735–43
2. Walmsley S, et al NEJM 2013 369: 1087-1818
3. Clotet, B.,et al. Lancet 2014; 383:2222-31
4. Sax P, et al. Lancet 2012; 379:2439-48
5. DeJesus E, et al. Lancet 2012; 379: 2429-38

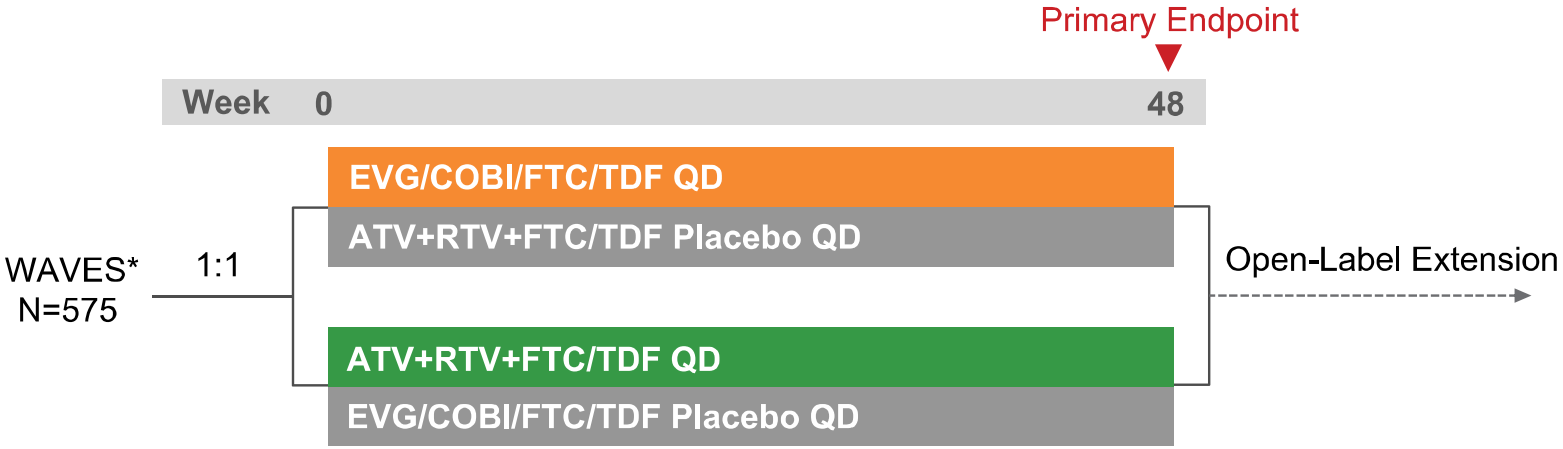
Efficacy By Backbone And In High Viral Load Patients At Week 48

Outcomes	SPRING-2[1]	SINGLE[2]	FLAMINGO[3]	Study 102[4]	Study 103[5]
	2 NRTI + DTG 50 mg QD	2 NRTI + + DTG 50 mg QD	2 NRTI + + DTG 50 mg QD	EVG/COBI/ FTC/TDF STR	EVG/COBI/ FTC/TDF STR
VS (%<50 copies/mL) In patients with VL> 100,000 copies/mL on TDF/FTC backbone (n/N)	81% (62/77)	N/A	94% (45/48)	84% (99/118)	85% (128/150)
VS (%<50 copies/mL) In patients with VL> 100,000 copies/mL on ABC/3TC backbone (n/N)	73% (27/37)	83% (111/134)	92% (12/13)	N/A	N/A

This slide reflects data from multiple clinical trials: the regimens have not been compared head-to-head in a clinical trial. No assertions on comparative clinical efficacy are made or inferred.

1. Raffi F, et al. Lancet Infect Dis 2013;381: 735–43
2. Walmsley S, et al NEJM 2013 369: 1087-1818
3. Clotet, B.,et al. Lancet 2014; 383:2222-31
4. Sax P, et al. Lancet 2012; 379:2439-48
5. DeJesus E, et al. Lancet 2012; 379: 2429-38

Study Design

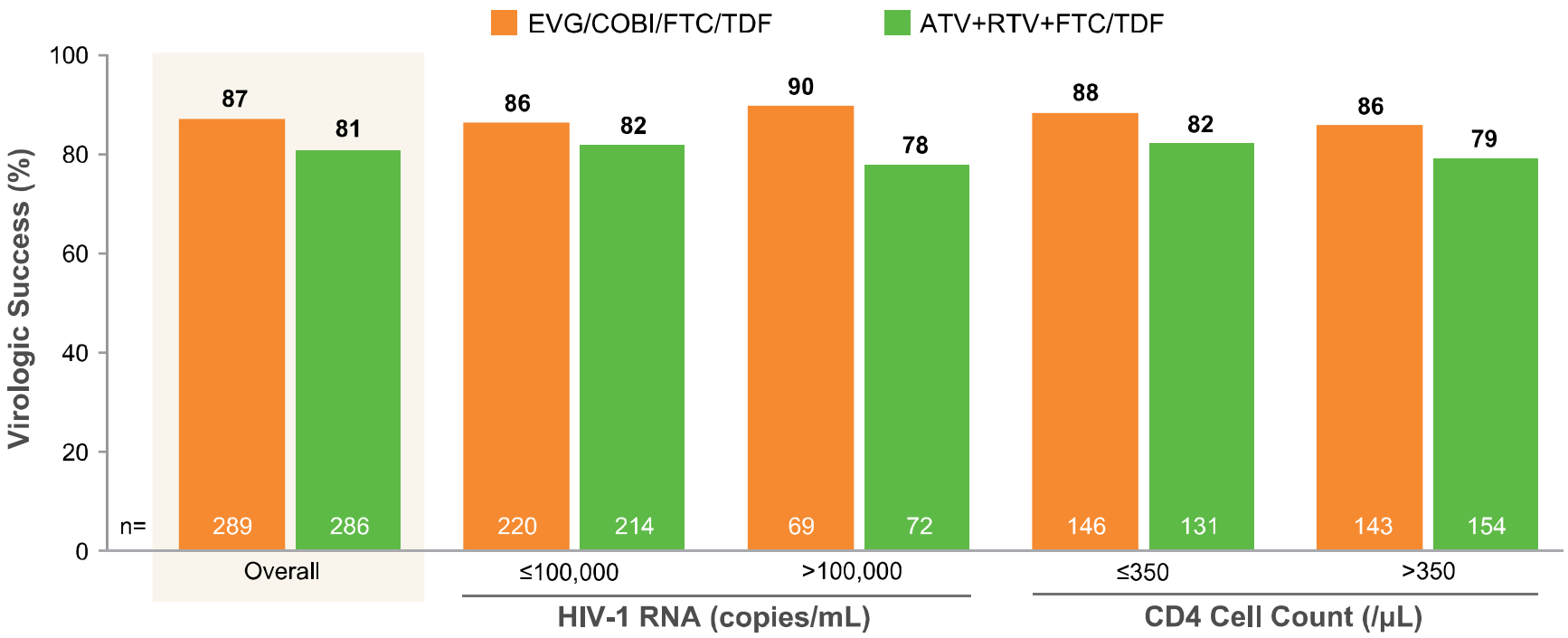


- Key eligibility criteria
  - HIV-1 RNA ≥500 copies/mL
  - Estimated glomerular filtration rate (eGFR) ≥70 mL/min
  - No history of ART
  - Sensitivity to FTC, TDF, and ATV
- Primary endpoint: proportion of patients with HIV-1 RNA <50 copies/mL at Week 48 (Food and Drug Administration [FDA] snapshot analysis)
- Stratification
  - HIV-1 RNA (≤100,000, >100,000–≤400,000, or >400,000 copies/mL)
  - Race (black or nonblack)

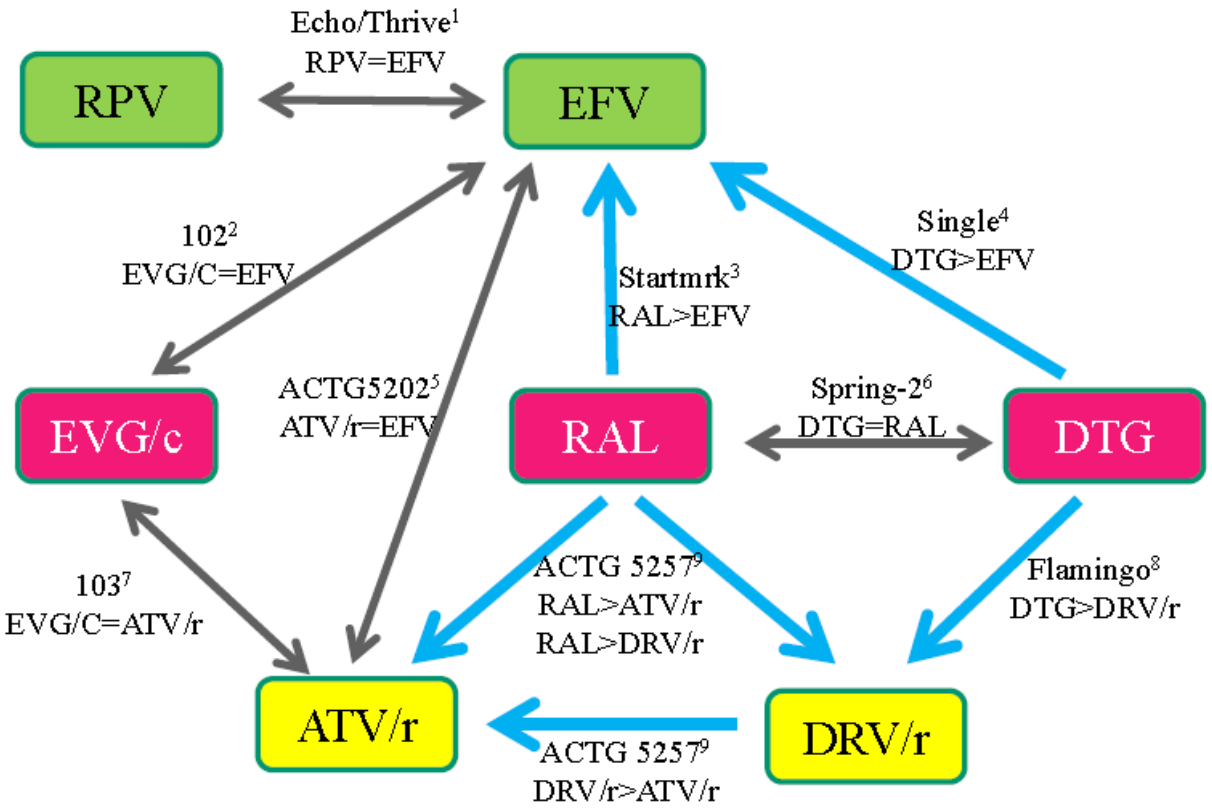
*Study ongoing.

Squires K, et al. IAS 2015, #MOLBPE08

Efficacy by Baseline HIV-1 RNA Levels and CD4 Count



Increasing evidence for integrase inhibitors in ART-naive patients



1. Cohen CJ et al. JAIDS 2012; 60 (1): 33-42 ; 2. Sax PE et al. Lancet 2012; 379: 2439–48; Rockstroh JK et al. JAIDS 2013; 63 (1); 4. Walmsley SL et al. N Engl J Med 2013; 369:1807-1818; 5. Daar ES, et al. Ann Intern Med 2011;154:445–56; 6. Raffi F et al. Lancet. 2013 Mar 2;381(9868):735-43; 7. DeJesus E, et al. Lancet 2012;379:2429–38; 8. Feinberg J et al. 52 ICAAC, September 9-12, 2012, H-1464a; 9. Landovitz RJ et al. CROI 2014. Abstract 85.

ISTITUTO NAZIONALE PER LO STUDIO DELLE MALATTIE INFETTIVE
IRCCS "LAZZARO SPALLANZANI"

U.O.S.D. Monitoraggio
Terapie Antiretrovirali
Dirigente Medico Responsabile Prof. Carlo-Federico Perno
Tel. 06 55170654/656 – Fax. 06 5594555

L

SDS

GENOTIPIZZAZIONE
MODULO DI RISPOSTA

MUTAZIONI NOTE:

PROTEASI: K20I, M36I, V82I, L89M

TRASCRITTASI INVERSA: NESSUNA

INTEGRASI: NESSUNA

ALTRE MUTAZIONI:

PROTEASI: I13V, K14R, I15V, E35D, R41K, H69K

TRASCRITTASI INVERSA: V35T, V60I, A98S, K122E/K, D123D/N, I135L, K173I, Q174K, D177E, T200E, Q207K, R211S, V245Q, E248D, D250E, A272P, T286A, A288G, E291D, V292I, I293V, E297A, D320E, D324E, I329V

INTEGRASI: K14R, V31I, M50I, L101I, K111R, T124A, T125A, G134N, K136T, V201I, T206S, Y227F, L234I, S255N, D256E, R269K

RISULTATO

PR: Presenza di quattro mutazioni secondarie
RT: Assenza di mutazioni note
INT: Assenza di mutazioni note

FARMACI POTENZIALMENTE EFFICACI:

PR: Tutti con boost di ritonavir
RT: Tutti
INT: Raltegravir

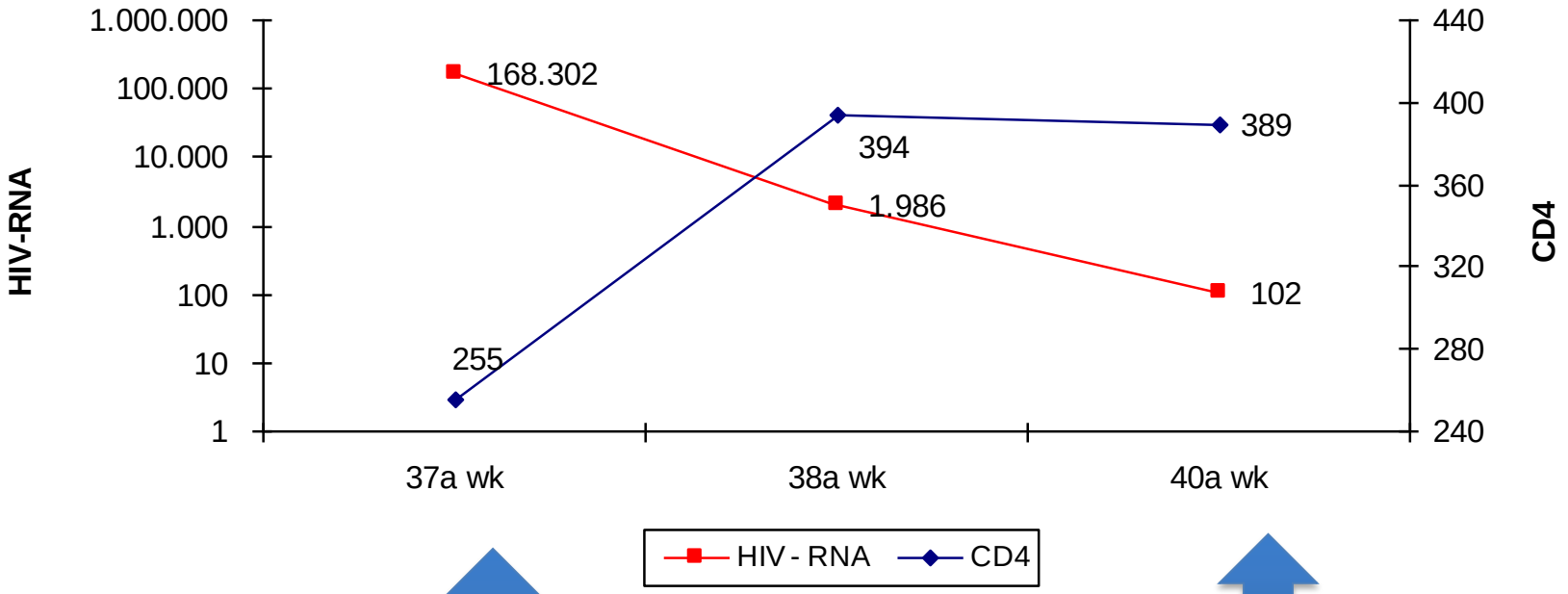
NOTE: Test eseguito in urgenza su gravida alla 36 settimana.
L'analisi filogenetica della sequenza nucleotidica del gene pol indica la presenza di sottotipo virale CRF02_AG

INTERPRETAZIONE : In un quadro genotipico wild type, si segnala la presenza nella proteasi di vari polimorfismi che possono essere correlati ad un incremento di rischio di sviluppo di resistenza agli inibitori della proteasi. Utile pertanto l'uso di inibitori della proteasi solo se potenti e con boost di ritonavir.

Il Responsabile

In data 13.01.2015 (37a sett.) inizia

Truvada, Reyataz, Norvir, Isentress



HAART

Profilassi neonatale: Retrovir+Epivir+ Viramune

HIV-DNA Bimbo: Negativo

T.C. 03.02 2015

Conclusions

- Amongst individuals who have achieved viral suppression on first line cART, higher baseline viral load and slower time to suppression are associated with a higher chance of subsequent virologic rebound
- Risk of rebound after initial suppression
  - is significantly lower with INSTI or NNRTI compared to PI.
  - depends mainly on high baseline VL and time to viral suppression ≥ 6 months for NNRTI and PI
  - depends only on time to viral suppression ≥ 6 months and not on high baseline VL for INSTI
    - Limitation : small sample size for INSTI sub-group

Le nuove sfide dell'HIV

Caso clinico

"Un paziente altoviremico"

Giuseppina Liuzzi

Istituto Nazionale per le Malattie Infettive

"Lazzaro Spallanzani"