Semplificazione e ottimizzazione della terapia ARV

Simona Di Giambenedetto

Università Cattolica del Sacro Cuore, Fondazione Policlinico Gemelli, IRCCS, ROMA

Disclosures

I have received funding for Advisory Boards, Speaker Panels and for preparation of educational materials from the following:

Gilead Sciences
ViiV Healthcare
Janssen-Cilag
Merck Sharp & Dohme

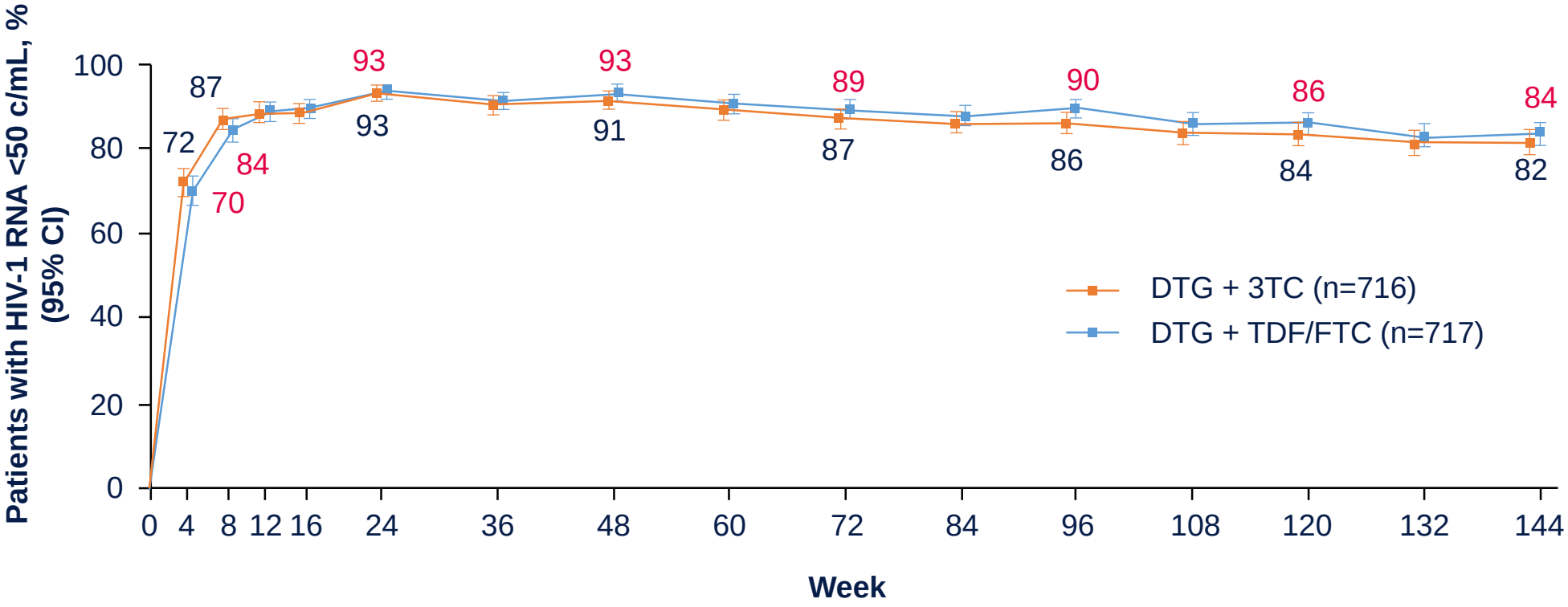
Linee guida EACS 2022

Regimen	Main requirements	Additional guidance (see footnotes)
Recommended regimens		
2 NRTIs + INSTI		
ABC/3TC + DTG ABC/3TC/DTG	HLA-B*57:01 negative HBsAg negative	I (ABC: HLA-B*57:01, cardiovascular risk) II (Weight increase (DTG))
TAF/FTC/BIC		II (Weight increase (BIC, TAF))
TAF/FTC or TDF/XTC + DTG		II (Weight increase (DTG, TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing)
TAF/FTC or TDF/XTC + RAL qd or bid		II (Weight increase (RAL, TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) IV (RAL: dosing)
1 NRTI + INSTI		
XTC + DTG or 3TC/DTG	HBsAg negative HIV-VL < 500,000 copies/mL Not recommended after PrEP failure	II (Weight increase (DTG)) V (3TC/DTG not after PrEP failure)
2 NRTIs + NNRTI		
TAF/FTC or TDF/XTC + DOR or TDF/3TC/DOR		II (Weight increase (TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VI (DOR: caveats, HIV-2)

EACS Guidelines – version 11.1 – October 2022

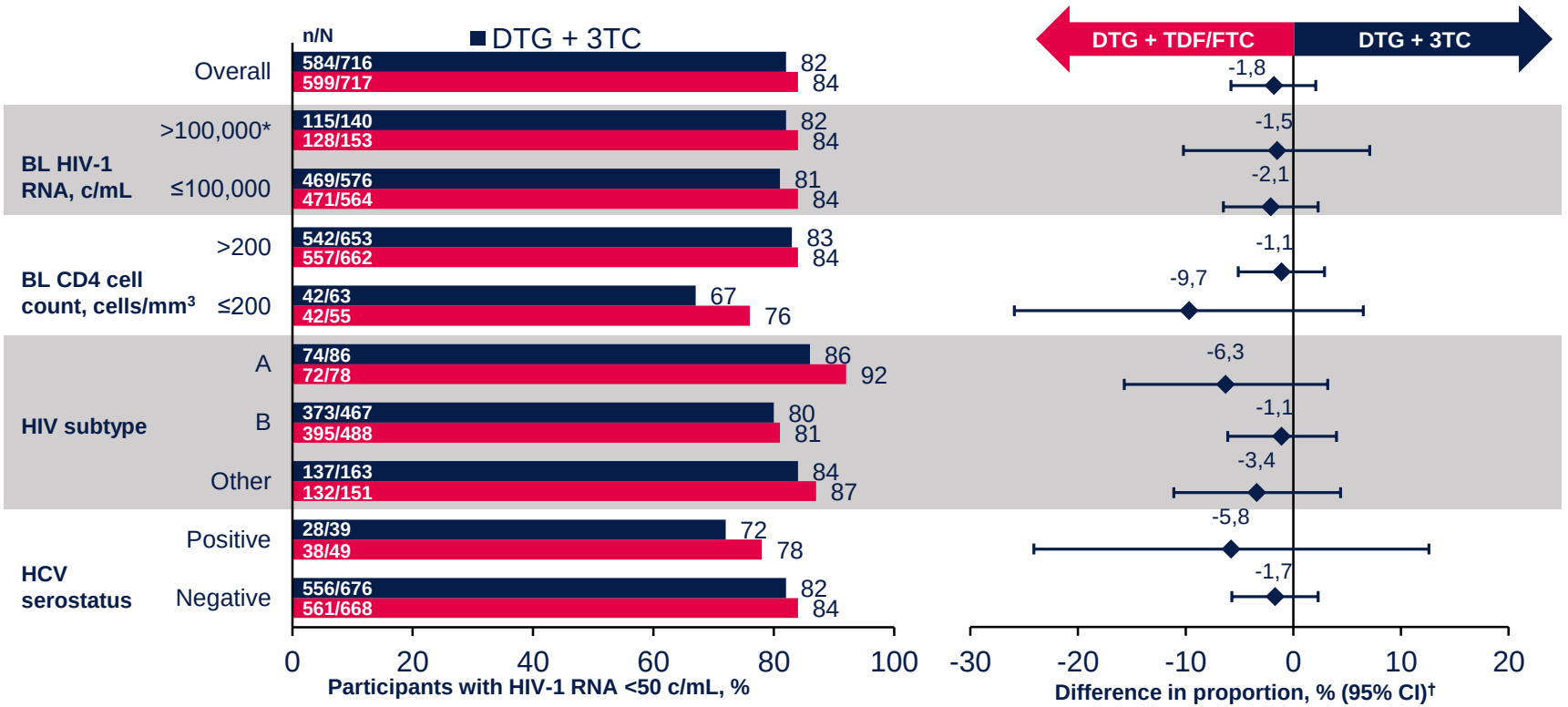
GEMINI-1 and -2: Pooled Snapshot Analysis Through Week 144 (ITT-E Population)

- DTG + 3TC was non-inferior to DTG + TDF/FTC in the pooled ITT-E population analysis through Week 144



Cahn P, et al. AIDS 2022;36:39–48

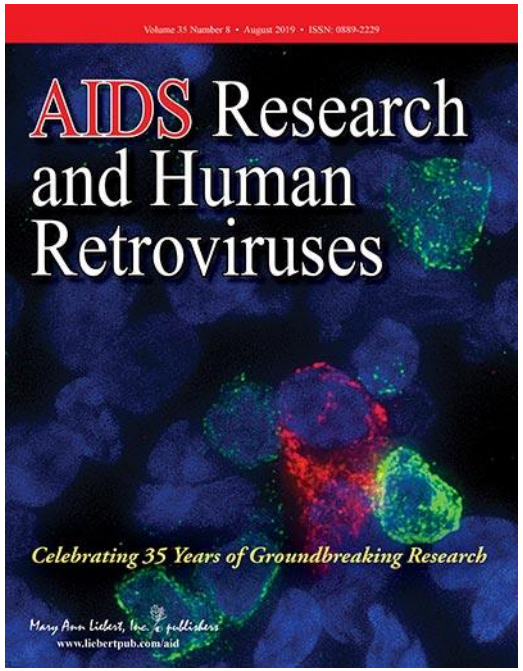
GEMINI-1 and -2: HIV-1 RNA <50 c/mL Across Baseline Disease Subgroups at Week 144



*Includes values for HIV-1 RNA >250,000 c/mL (DTG + 3TC, 41/51 [80%]; DTG + TDF/FTC, 37/46 [80%]), HIV-1 RNA >400,000 c/mL (DTG + 3TC, 15/18 [83%]; DTG + TDF/FTC, 19/24 [79%]), and HIV-1 RNA >500,000 c/mL (DTG + 3TC, 10/13 [77%]; DTG + TDF/FTC, 12/15 [80%]); †Adjusted difference for overall population (DTG + 3TC − DTG + TDF/FTC), unadjusted difference for subgroups calculated by proportion on DTG + 3TC − proportion on DTG + TDF/FTC

Orkin C, et al. CROI 2021. Slides 1991

DTG+3TC Come dati di prima linea: DATI DI REAL LIFE



Efficacy and safety of dolutegravir plus lamivudine as a first-line regimen in clinical practice

A. Ciccullo et al. AIDS Research and Human Retroviruses 2021

Studio osservazionale retrospettivo

Abbiamo analizzato 20 pazienti: 15 di sesso maschile, con età mediana di 35 anni (IQR 25-54).

Al baseline, la mediana di HIV-RNA era di 4.78 $\log_{10}$ copie/mL mentre la conta mediana dei linfociti CD4+ era di 342 cell/mm^3 (IQR 239-472).

Cinque pazienti avevano un valore basale di HIV-RNA superiore a 100.000 copie/mL ma sotto le 500.000 copie/mL.

A. Ciccullo et al. AIDS Research and Human Retroviruses 2021

During a cumulative time of 15.4 Patient-Years of Follow-Up, we did not observe any adverse event or treatment discontinuation in our cohort. All patients achieved virological suppression in the first 6 months from treatment initiation and maintained viral suppression during follow-up time with no viral blips registered.

Increase in CD4+ cells was significant at both week 24 (p=0.003) and week 48 (p=0.007) of follow-up. We observed that, at a multivariate analysis, **a lower age was associated with a greater increase in CD4+ cells after 48 weeks** (per 10 years younger, B -63.8, 95%CI -122.7 to -4.9, p=0.039). Moreover, **CD4/CD8 ratio also significantly improved** during follow-up: we registered a median increase of +0.12 (p=0.005) after 24 weeks and +0.22 (p=0.028) after 48 weeks of follow-up.

A. Ciccullo et al. AIDS Research and Human Retroviruses 2021

We further investigated patients' virological status by evaluating total HIV-1 DNA levels at baseline and at virological suppression in 11 patients (55% of our population).

In this subgroup, viral suppression was achieved after a median time of **68.2 days** with a median HIV-1 DNA at baseline of 3.85 log/10^6 CD4 and a median HIV-1 DNA decrease of 0.47 log/10^6 CD4 between baseline and viral suppression.

The observed decline rate was similar to the ones observed in PLWHIV starting a 3-drug based first-line regimen, suggesting that DTG+3TC may be equally effective in reducing proviral HIV-DNA and, thus, inflammation levels.

A. Ciccullo et al. AIDS Research and Human Retroviruses 2021

COVID-19

Retrospective Analysis, Monogram Biosciences (US and Puerto Rico)

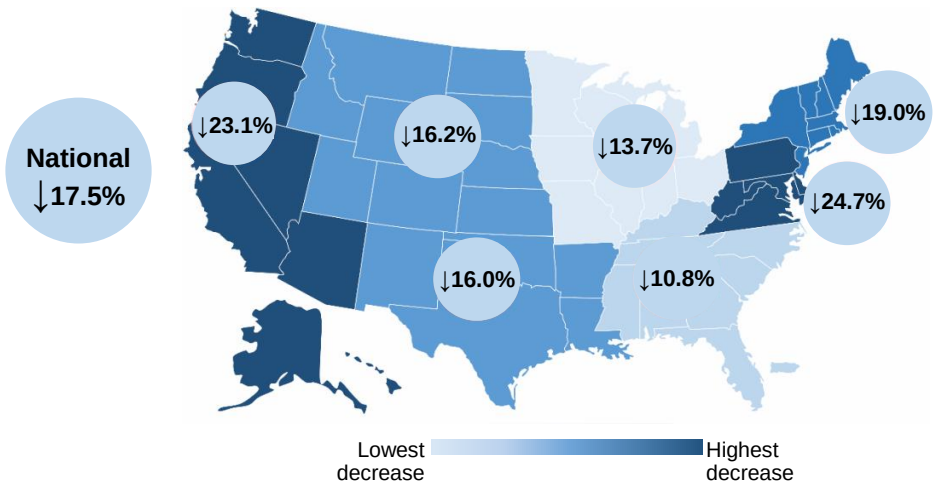
HIV Testing During the COVID-19 Pandemic

HIV diagnostic test volume | HIV positivity | Acute infection

Outcomes
Percent change in HIV diagnostic test volume, HIV positivity rate and acute infection rate by region, gender and/or age

Mar–Oct 2020
vs. Mar–Oct 2019

Change in HIV Diagnostic Test Volume from 2019 to 2020, by Region



HIV Positivity and Acute Infection Rates

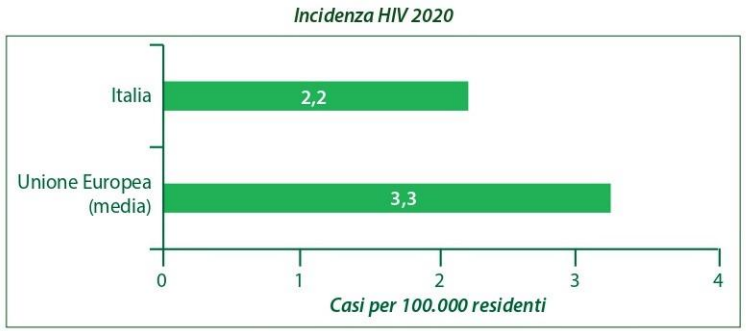
	HIV positivity			Acute HIV infection		
Region or demographic	**2019 (%)**	**2020 (%)**	***P*-value**	**2019 (%)**	**2020 (%)**	***P*-value**
US and Puerto Rico	**0.68**	**0.66**	**0.023**	**1.15**	**0.91**	**0.016**
Northeast*	0.57	0.55	0.221	0.91	0.49	0.089
Mid-Atlantic†	0.50	0.51	0.772	1.08	1.15	0.795
Midwest‡	0.49	0.49	0.816	1.06	1.78	0.112
South Central§	0.95	0.89	0.004	0.78	0.74	0.848
Southeast¶	0.85	0.76	<0.0001	1.37	0.81	0.002
Mountain‖	0.36	0.34	0.621	1.07	1.33	0.784
West#	0.57	0.66	<0.0001	1.54	1.05	0.111
Male	**1.41**	**1.48**	**<0.0001**	**1.15**	**0.22**	**<0.0001**
<25 years	0.82	0.97	<0.0001	2.85	2.31	0.344
25–40 years	1.50	1.60	0.0002	1.27	0.90	0.035
41–55 years	1.48	1.51	0.496	0.79	0.73	0.781
>55 years	1.57	1.63	0.138	0.58	0.29	0.091
Female	**0.26**	**0.23**	**<0.0001**	**1.14**	**0.97**	**0.433**
<25 years	0.07	0.08	0.401	2.11	5.61	0.028
25–40 years	0.16	0.15	0.003	1.81	1.00	0.055
41–55 years	0.49	0.47	0.169	0.64	0.44	0.442
>55 years	0.71	0.69	0.536	0.73	0.29	0.146

Blue = significant increases; Red = significant decreases

Diagnostic HIV test volume, positivity and acute infection rates decreased during the COVID-19 pandemic with regional and gender-based differences noted

*CT, MA, ME, NH, NJ, NY, RI, VT; †DC, DE, MD, PA, VA, WV; ‡IA, IL, IN, KS, MI, MN, MO, NE, OH, WI; §AR, LA, NM, OK, TX; ¶AL, FL, GA, KY, MS, NC, PR, SC, TN; ‖CO, ID, MT, ND, SD, UT, WY; #AK, AZ, CA, HI, NV, OR, WA

EPIDEMIOLOGIA ITALIA



Incidenza HIV: numero di nuove diagnosi HIV per 100.000 residenti (Italia e Unione Europea).
Fonti: Sistema di Sorveglianza HIV nazionale, *ECDC/WHO 2021 HIV/AIDS Surveillance in Europe 2021-2020 data*

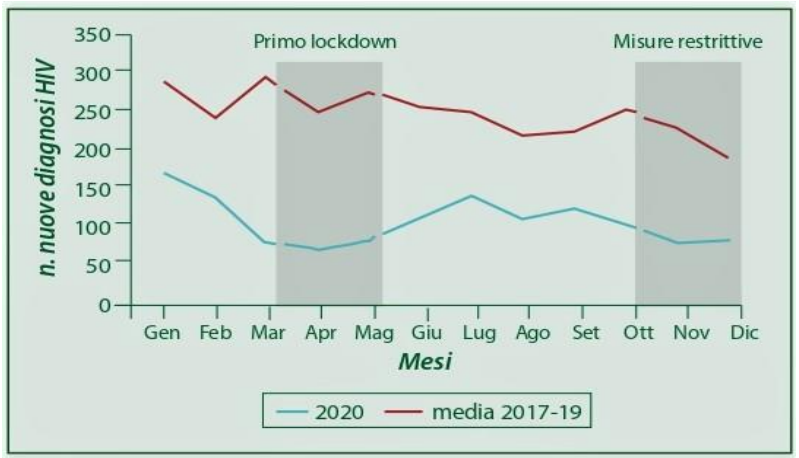
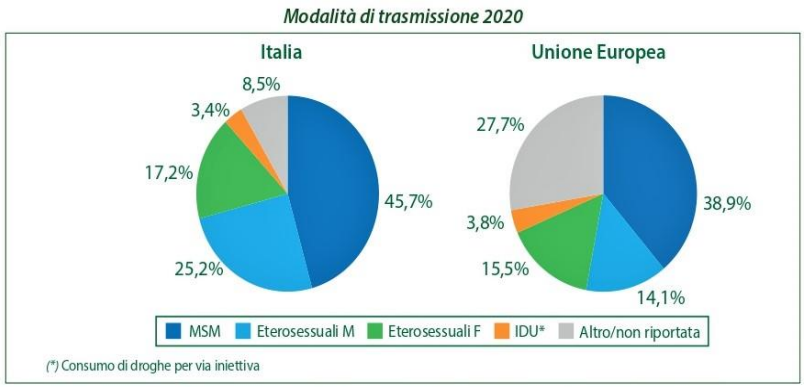
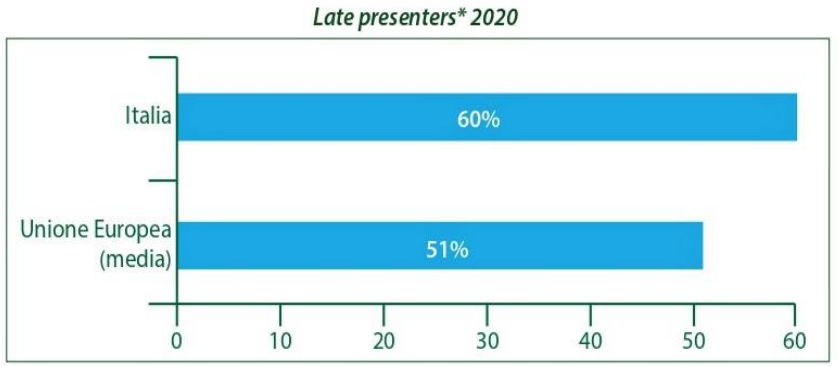


Figura 1 - Andamento delle nuove infezioni da HIV per mese di diagnosi



Distribuzione percentuale delle nuove diagnosi di infezione da HIV per modalità di trasmissione 2020
Fonti: Sistema di Sorveglianza HIV nazionale, *ECDC/WHO 2021 HIV/AIDS Surveillance in Europe 2021-2020 data (1)*



(*) Late presenters: nuove diagnosi di infezione da HIV con numero di linfociti CD4 < 350 cell/µl
Fonti: Sistema di Sorveglianza HIV nazionale, *ECDC/WHO 2021 HIV/AIDS Surveillance in Europe 2021-2020 data (1)*

Comparing the efficacy and safety of a first line regimen with emtricitabine/tenofovir alafenamide fumarate plus either bictegravir or dolutegravir: results from clinical practice

A. Ciccullo et al. IJAA submitted

Variables	BIC group (n=187)	DTG group (n=140)	p
Age, median (IQR)	42 (33-52)	45 (34-55)	0.088
Male sex, n (%)	149 (79.7)	114 (81.4)	0.351
HIV risk factors: - MSM - Heterosexual - IDUs - Other/Unknown	 84 (44.9) 89 (47.6) 6 (3.2) 8 (4.3)	 70 (50.0) 45 (32.1) 8 (5.7) 17 (12.1)	0.001
CDC stage C, n (%)	34 (18.2)	22 (15.7)	0.461
Median log10 HIV-RNA copies/ml (IQR)	4.97 (4.28-5.51)	5.31 (4.65-5.76)	0.005
Median CD4+ cell at baseline (IQR)	340 (130-553)	120 (30-358)	<0001
Median CD4/CD8 ratio	0.25 (0.09-0.40)	0.17 (0.07-0.23)	0.275
HCV coinfected	4 (2.1)	2 (1.4)	0.351
HBV coinfected	3 (1.6)	1 (0.7)	0.594
Primary infection	12 (6.4)	2 (1.4)	0.517

Results/ Snapshot virological efficacy 6m

- At 6 months, among PLWHIV with available exams, 85.7% of individuals in the DTG group and 87.2% of those in the BIC group achieved a HIV-RNA below 50 copies/mL.
- **Considering those achieving TND at 6 months, 39% of those with DTG vs 13% of those in the BIC group (p<0.001).**
- *Starting BIC (vs DTG) was significantly associated with a lower probability of achieving TND after 6 months (OR 0.23, 95%CI 0.12-0.45, p<0.001)*
- In the BIC group, starting with a higher CD4+ cell count was associated with higher probability of TND after 6 months (per 100 cell more, B 0.3, aHR 1.01, p=0.022)

Results/ Snapshot virological efficacy 12m

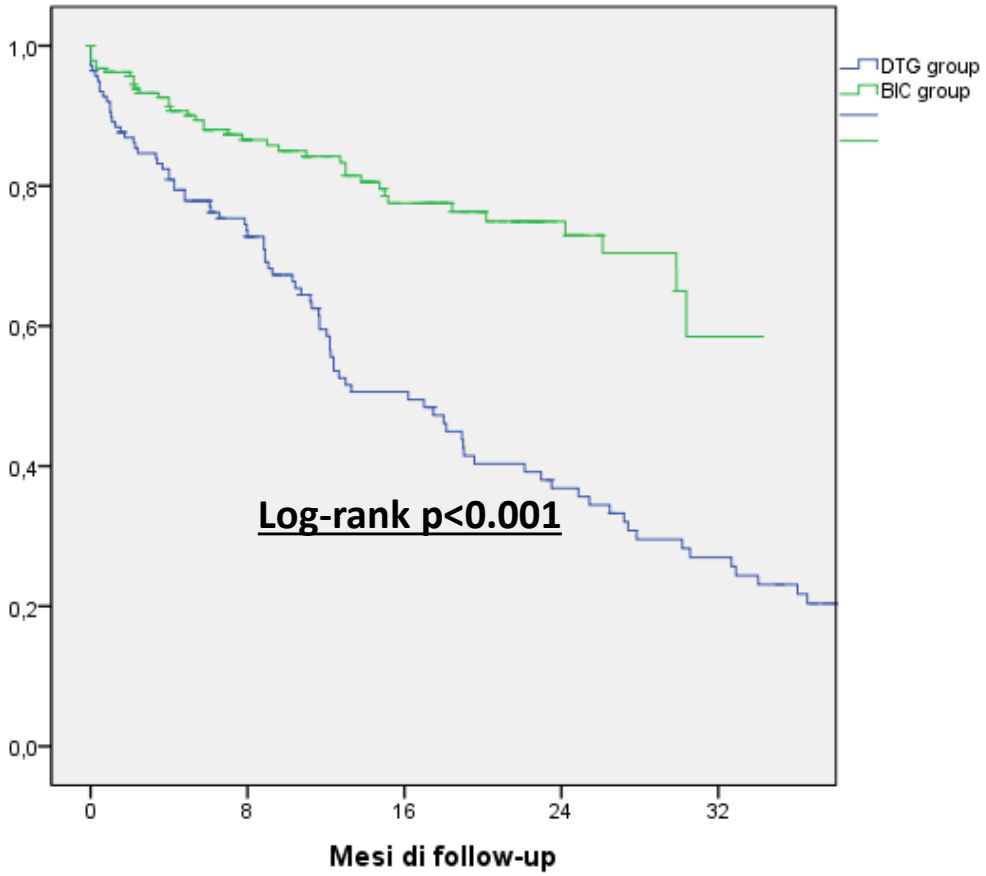
- At 12 months, 90.0% of individuals in the DTG group and 86.7% of those in the BIC group achieved a HIV-RNA below 50 copies/mL.

- **Considering those achieving TND at 12 months, 54% of those with DTG vs 17% of those in the BIC group (p<0.001).**

- *Starting BIC (vs DTG) was significantly associated with a lower probability of achieving TND after 12 months (OR 0.18, 95%CI 0.09-0.34, p<0.001)*

- In the BIC group, starting with a higher CD4+ cell count was associated with higher probability of TND after 6 months (per 100 cell more, B 0.6, aHR 1.01, p=0.001)

Results/TD

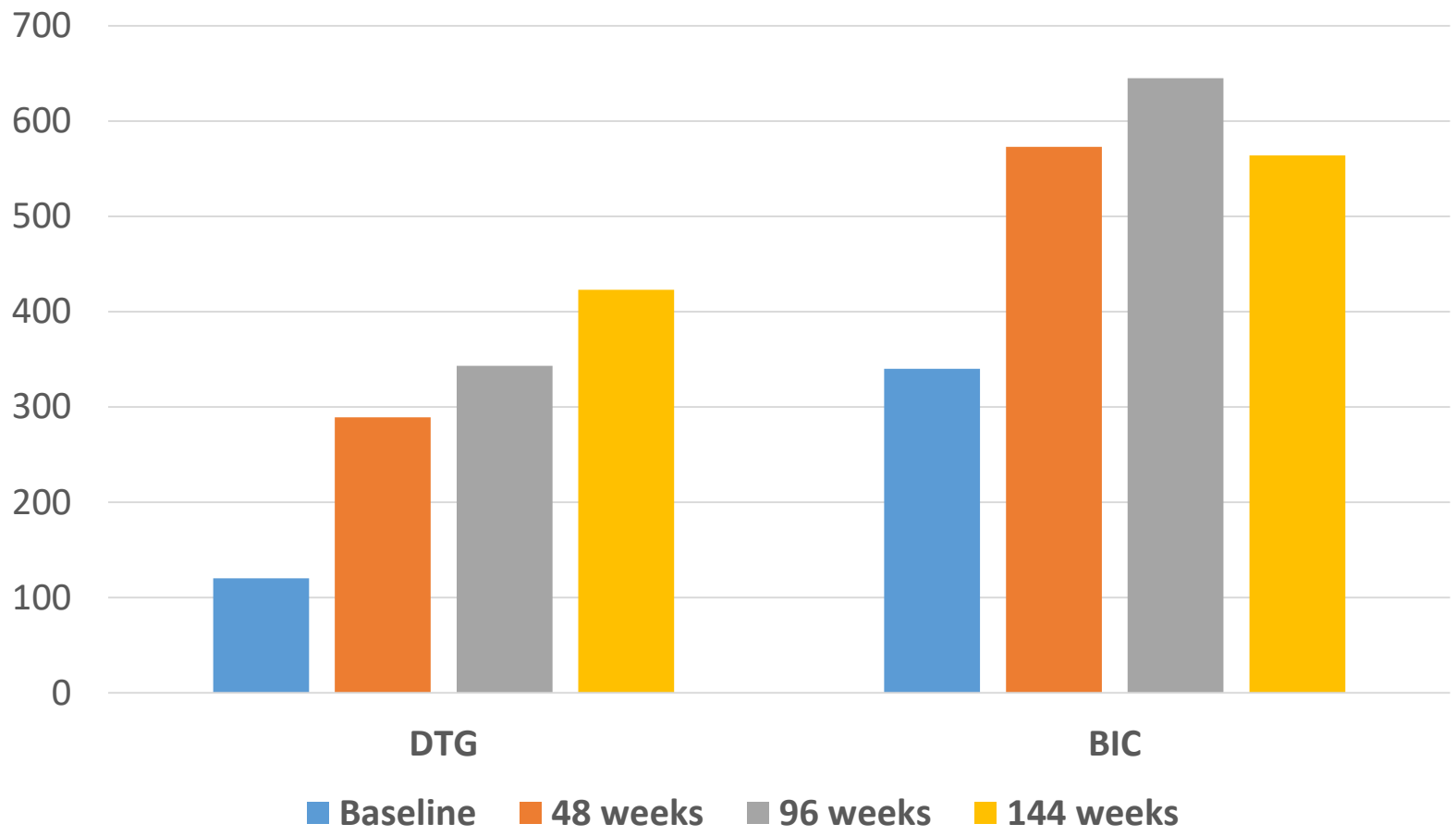


We observed 88 TD in the DTG group and 38 in the BIC group.

In the **DTG** group, main reasons for TD were: **switch to STR/2DR in 36% of PLWHIV**, CNS toxicity (5.0) and death (4.3).

In the **BIC** group main reasons were: switch to 2DR (11.3), Hypersensitivity (2.1), NON-CNS toxicity (2.1)

Results/Immunological



Come scegliere la terapia nei pazienti soppressi

- Ottima tollerabilità
- Buona efficacia
- Ridotti costi

Terapia personalizzata

Ottimizzazione a viremia soppressa (LG EACS 2022)

- La prolungata sopravvivenza dei pazienti HIV+, garantita dai moderni farmaci antiretrovirali, ha consentito di constatare l'importanza dell'ottimizzazione della terapia, al fine di:

- Ovviare a una tossicità in atto (switch reattivo);
- Prevenire una tossicità prevedibile (switch preventivo o proattivo);
- Evitare il rischio di interazioni farmacologiche;
- Ridurre il pill-burden;
- Migliorare la compliance.

Le strategie di ottimizzazione possono prevedere la riduzione del numero di compresse **(STR)** o la riduzione del numero di molecole **(2DR)**

Considerazioni da effettuare al momento dello switch

Drug Resistance:

- Review ART history for possible VF
- Review all available resistance test results
- If earlier resistance uncertain, only consider switch if new regimen likely to maintain suppression of resistant virus
- Within-class switches usually maintain virologic suppression if no resistance to drugs in that class are present
- Caution when switching from boosted PI to another class if full treatment/resistance history not known
- Consult an expert when switching if resistance to ≥ 1 class

Safety:

- Review ART history for intolerance
- Must be HLA-B*5701 negative if considering ABC
- Consider drug–drug interactions with comedications

Comorbidity:

- HBV coinfection
- Cardiovascular disease or risk
- Renal function
- Bone mineral density
- Pregnancy
- Other coinfections

Modificata da DHHS ART Guidelines. December 2019.

Slide credit: clinicaloptions.com

Schemi di semplificazione

	EACS 11.1 (Oct 2022)	DHHS (Sep 2022)	Linee guida SIMIT (2017)
DTG + RPV	**Supported by large trials**	**AI**	**AI**
3TC + DTG	**Supported by large trials**	**AI**	BII
3TC + bATV	Supported by large trials	CI	**AI→switch da PI** BI→ switch da altre classi
3TC + bDRV	Supported by large trials	BI/BIII	**AI→switch da PI** BI→ switch da altre classi
RPV+CAB	**Supported by large trials**	**AI**	
3TC + bLPV	na	CI	na
DRV + RPV	Supported by small trials	na	CI
DTG + bDRV	Supported by small trials	CI	na
DRV + RAL	na	na	CI

HIV MEDICINE

British HIV Association
BHIVA

Lamivudine-based maintenance antiretroviral therapies in virologically-suppressed HIV-positive patients: derivation of a predictive score of virological failure

Borghetti et al. 2019

Algoritmo applicabile nella routine clinica che tiene conto di:

- Caratteristiche del ceppo virale (Sottotipo)
- Mutazione 184+TAM (Borghetti et al. OFID 2021)
- Storia immunovirologica del paziente (Nadir CD4+ , tempo dalla diagnosi e di soppressione virologica)
- Condizioni attuali (HIV-RNA allo switch non rilevabile)
- HIV-DNA (Borghetti et al. Submitted Viruses 2022)

DTG+3TC nello switch: 5 anni dopo

Five years with dolutegravir plus lamivudine as a switch strategy: much more than a positive finding

Ciccullo A et al. JAIDS NOV 201

Variables	N= 785
Age (years), Median (IQR)	52.3 (44.9 – 58.2)
Female, n (%)	231 (29.4)
Risk factor for HIV infection, n (%): - Heterosexual - MSM - IDU - Others	 319 (40.6) 305 (38.9) 119 (15.2) 42 (5.3)
Anti-HCV antibodies positive, n (%)	64 (12.9)
Time from HIV diagnosis (years), Median (IQR)	14.9 (8.0 – 22.0)
CDC stage C, n (%)	132 (16.9)
Time on antiretroviral therapy (years), Median (IQR)	11.5 (5.9 – 18.6)
Nadir of CD4+ (cell/µL), Median (IQR)	225 (96 - 331)
Zenith HIV-RNA (log copies/mL), Median (IQR)	4.94 (4.39 – 5.45)
Zenith HIV-RNA > 500.000 copies/mL, n (%)	110 (14.0)
Previous virological failure, n (%)	175 (22.3)
CD4+ count (cell/µL), Median (IQR)	680 (500 - 889)
Time of virological suppression (months), Median (IQR)	29.1 (14.6 – 49.5)
M184V resistance mutation, n (%) - Present - Absent - Unknown	 33 (4.2) 214 (27.3) 538 (68.5)
Previous HAART regimen, n (%): - 2NRTIs+NNRTI - 2NRTIs+PI or b/PI - 2NRTIs+INI - Dual therapy - Other	 180 (22.9) 92 (11.7) 216 (27.5) 268 (34.1) 29 (3.7)

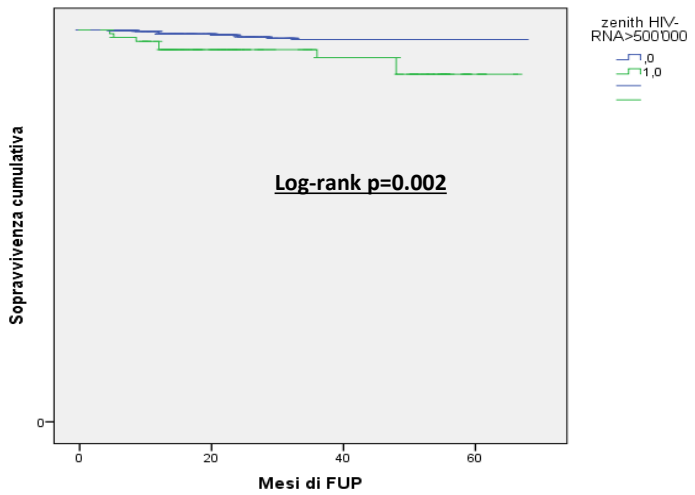
Variables	
FTC/TDF in previous regimen, n (%)	253 (32.3)
DTG in previous regimen, n (%)	147 (18.7)
3TC + PI in previous regime, n (%)	216 (27.5)
Reasons for switch, n (%): - Simplification - Dyslipidemia - Gastrointestinal or liver toxicity - Renal toxicity - Osteoporosis - Neurological toxicity - Other toxicities - Drug-drug interactions - Cardiovascular risk - Other/Unknown reasons	 302 (38.5) 96 (12.2) 49 (6.2) 32 (4.1) 27 (3.4) 6 (0.8) 28 (3.6) 50 (6.4) 21 (2.7) 174 (22.2)

Risultati

- Conferma eccellente efficacia virologica. Probabilità di mantenere la soppressione virologica del 97.7% a 24 mesi e 96.4% a 60 mesi.

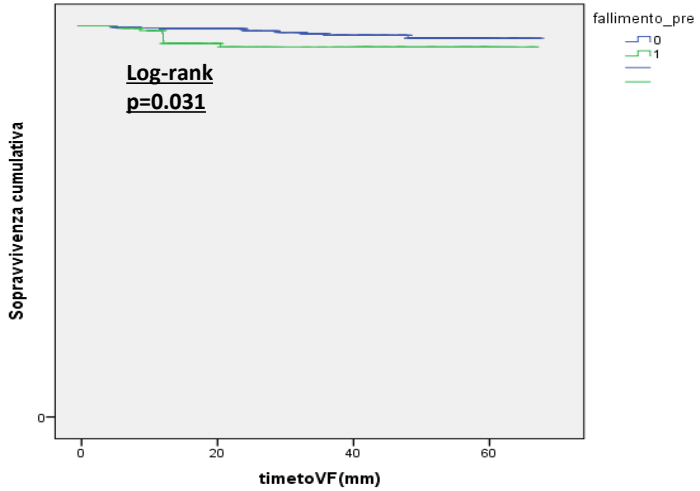
- Probabilità di non interrompere il regime è risultata essere del 82.9% a 2 anni, 79.7% a 3 anni, 78.0% a 4 anni, 74.3% a 5 anni.

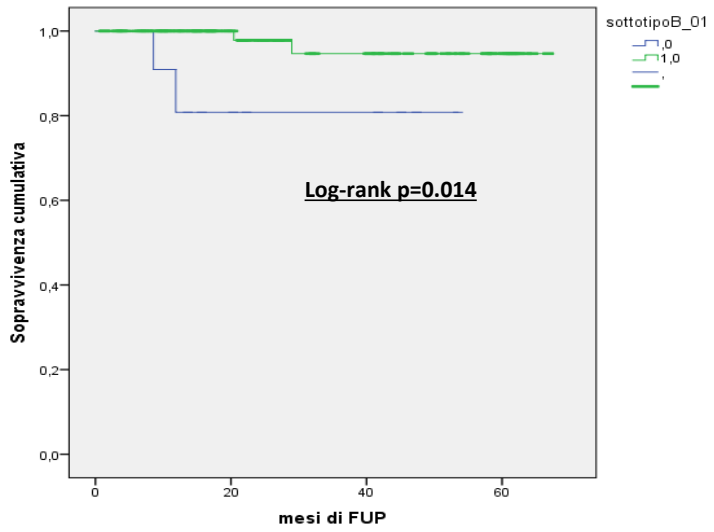
- Incremento dei CD4+ significativo a 1 anno (+27 cell/mm3, $p<0.001$), 2 anni (+30 cell/mm3, $p=0.001$) e 3 anni (+11 cell/mm3, $p=0.038$). Incremento mediano a 5 anni di 49 cell/mm3 ($p=0.073$).



In pazienti con Zenith HIV-RNA oltre 500.000 copie/ml, la probabilità di evitare fallimento virologico a 3 anni è risultato del 92.9%, rispetto al 97.6% dell'altro gruppo

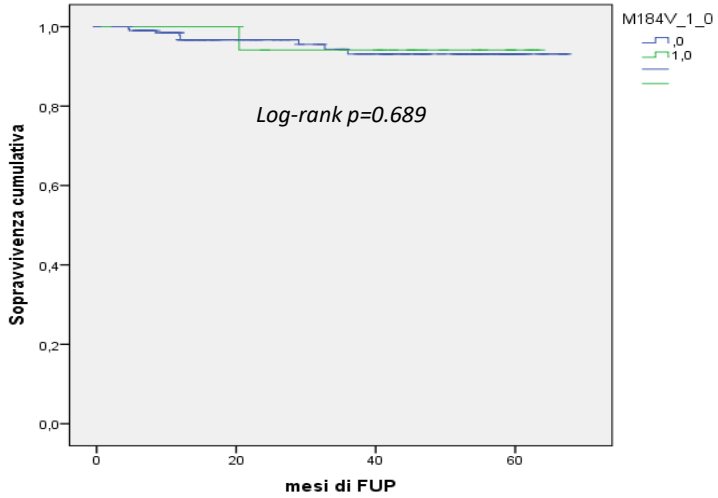
In pazienti con pregresso fallimento virologico, la probabilità di evitare fallimento virologico a 2 anni è risultato del 94.6%, rispetto al 98.7% dell'altro gruppo





In pazienti con sottotipo B, la probabilità di evitare fallimento virologico a 2 anni è risultato del 97.8%, rispetto al 80.8% dell'altro gruppo

Non differenze significative in pazienti con M184V rispetto agli altri in termini di rischio di fallimento virologico.



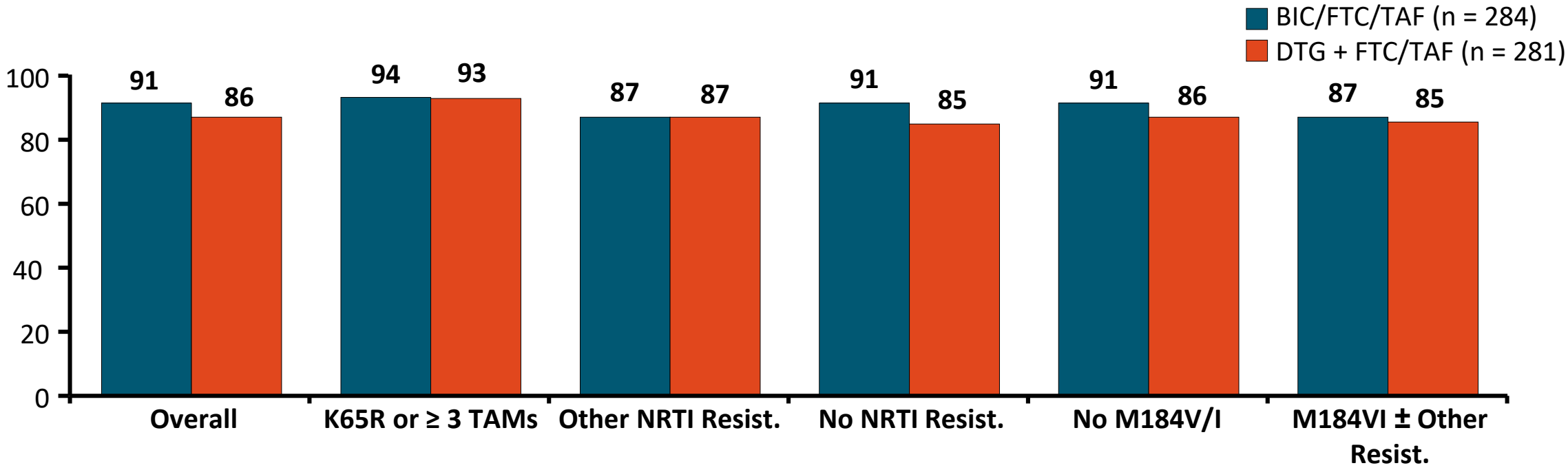
DHHS: regimi di switch in pazienti con storia di resistenze pregresse

- *"Patients with prior drug resistance can be switched to a new regimen based on their ARV history and resistance testing results"*
- Alcuni dati supportano lo switch intra-classe (DTG → BIC): Studio 380-4030
- Nessun dato diretto per lo switch tra classi da un regime ad alta barriera a un altro (da boosted PI a BIC o DTG)
  - Supporto teorico dallo studio 380-4030
  - Supporto indiretto dallo studio di superiore efficacia di DTG confrontato con LPV nei pazienti con fallimento a prima linea terapeutica e resistenze: studio DAWNING

DHHS ART Guidelines. December 2019.

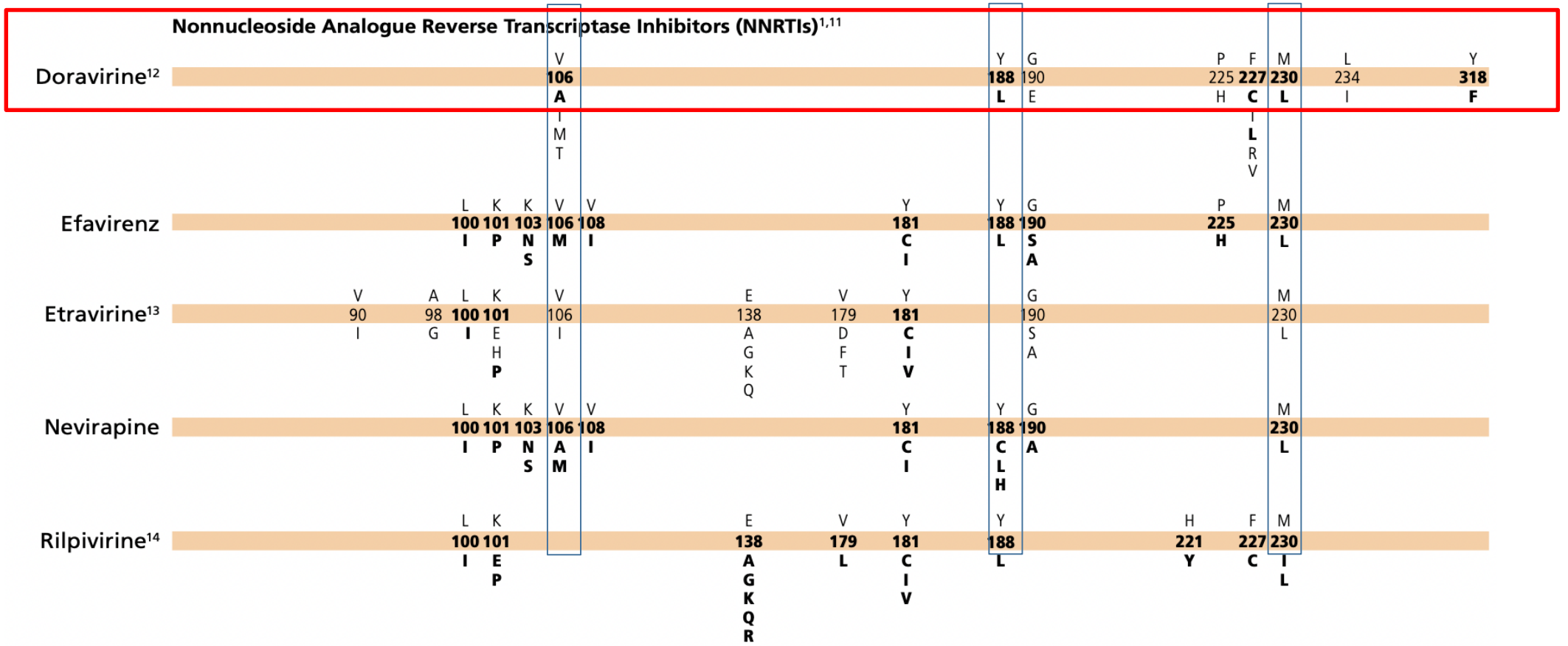
Study 380-4030: Viral Suppression After Switch From DTG to BIC by Baseline NRTI Resistance

- HIV-1 RNA ≥ 50 c/mL not observed in any patient with preexisting NRTI resistance



Data suggest switching 1 high-resistance barrier drug for another may be effective in patients with viral suppression, even in the setting of underlying resistance

Doravirina e mutazioni di resistenza



Resistance mutation list, IAS 2022

Real-Life Safety of Doravirine in Treatment-Experienced, Virologically Suppressed PLWHIV

- 33 HIV patients followed in outpatient setting
- Inclusion criteria: Patients who are virologically suppressed and switch to a DOR based regimen
- Primary outcome: time to doravirine-discontinuation for any cause

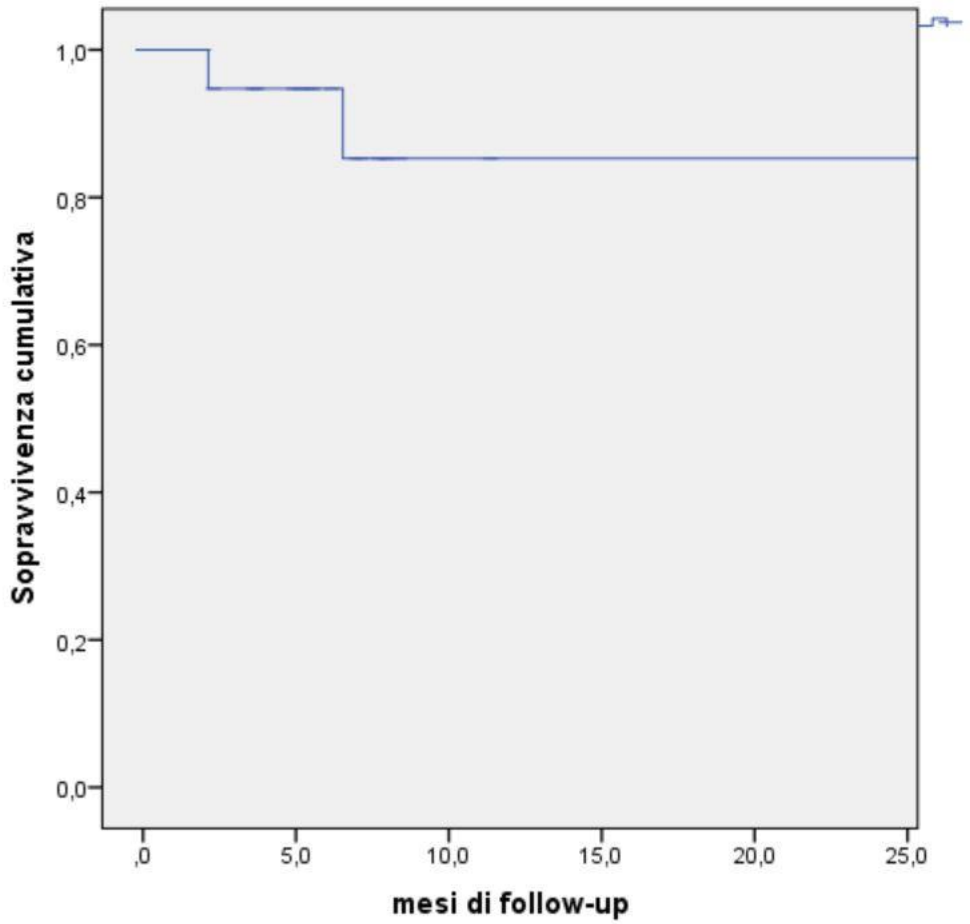
V. Iannone et al. JAIDS 2021

Caratteristiche della popolazione al baseline

Variables	N=33
Age, median (IQR)	52.9 (46.5 – 59.5)
Male sex, n (%)	22 (66.7)
HIV risk factor:	
- **Heterosexual**	12 (36.4)
- **MSM**	17 (51.5)
- **IDU**	4 (12.1)
Years of HIV infection, median (IQR)	11.3 (4.9 – 21.8)
Years of ARV exposure, median (IQR)	11.1 (4.8 – 18.4)
CDC Stage C, n (%)	14 (42.4)
Previous virological failure, n (%)	8 (24.2)
HBsAg+, n (%)	3 (9.1)
HCV Antibodies, n (%)	4 (12.1)
CD4+ cell count nadir, median (IQR)	118 (43 - 275)
Zenith HIV-RNA, median (IQR)	5.32 (4.60 – 5.65)
Previous RPV exposure, n (%)	25 (75.8)

Pre-switch regimen:	
- 2NRTI + INI	12 (36.4)
- 2NRTI + NNRTI	11 (33.3)
- 2NRTI + PI	8 (24.2)
- Other	2 (6.1)
Reason for starting DOR:	
- Proactive switch	27 (75.1)
- Toxicity	3 (8.3)
- Naive	3 (8.3)
- Other	3 (8.3)

Sopravvivenza del regime



Nella nostra analisi, a 6 e 12 mesi di follow-up, la probabilità di proseguire DOR è risultata pari a 93.8% e 80.4%, rispettivamente

Sono state osservate 3 interruzioni durante 167.1 PMFU: una per fallimento virologico e due per intolleranze gastrointestinali.

Resistenze

Al genotipo storico, 5 pazienti (13.9%) presentavano una resistenza maggiore agli NNRTI:

- 3 pazienti E138A
- 1 paziente K103N
- 1 paziente Y188L

Nessuno dei pazienti con mutazione agli NNRTI ha interrotto il regime con DOR né ha presentato rialzi di HIV-RNA.

☑ All RECOMMENDATIONS: USE OF INJECTABLE CAB/RPV LA AS REPLACEMENT ART IN VIRALLY SUPPRESSED ADULTS

Patients for Whom CAB/RPV LA Is Not Recommended

- Before recommending a switch to CAB/RPV LA, clinicians should determine patients' hepatitis B status (hepatitis B surface antigen, core antibody, surface antibody, and HBV DNA if indicated); CAB/RPV LA should not be recommended for patients with active HBV coinfection [a] without concurrent oral therapy for HBV. (A*)
- Before recommending CAB/RPV LA for patients who have been treated previously with INSTIs or NNRTIs, clinicians should review results of prior resistance testing and ART treatment history or consider baseline genotypic resistance testing if no prior results are available; genotypic resistance testing should include both the reverse transcriptase and integrase genes. (A3)
- Clinicians should not recommend CAB/RPV LA in patients with known or suspected INSTI or NNRTI RAMs, excluding the K103N mutation in isolation, at baseline. (A1)
- Because there are no currently available data on the safety and efficacy of this regimen in children or adolescents or during pregnancy or breastfeeding, clinicians should not recommend treatment with CAB/RPV LA for these patients. (A*)
- Preexisting CAB and RPV RAMs have been associated with virologic failure; therefore, clinicians should obtain proviral DNA genotypic resistance testing before switching to CAB/RPV LA in any patient for whom historical resistance test results are not available. (B2)

Administration

- CAB/RPV LA should be administered by a licensed and trained healthcare professional. (A*)
- To prepare and administer CAB/RPV LA, clinicians should follow the protocols detailed in Box 2 and in the medication package inserts. (A1)

Dosing Strategy

- If an oral lead-in is chosen to assess medication tolerability, the clinician should prescribe up to 4 weeks of oral CAB/RPV. (A3)
- Once a dosing schedule is decided upon, clinicians should administer CAB/RPV LA as detailed in *Table 2: Optional Lead-in, Initiation, and Maintenance for Monthly CAB/RPV LA Dosing* or *Table 3: Optional Lead-in, Initiation, and Maintenance for Bimonthly CAB/RPV LA Dosing*; a bimonthly (every 8 weeks) dosing schedule is preferred. (A1)

Managing Missed Injections

- If a patient plans to miss or delay a monthly CAB/RPV LA injection by >7 days, the clinician should arrange for oral medication (CAB 30 mg and RPV 25 mg daily) to be available in advance in an adequate supply (up to 2 months/8 weeks) to cover the gap in injections.
- Clinicians should resume CAB/RPV LA in patients who miss injections as detailed in *Managing Missed or Delayed Injections*. (A3)

DHHS/NYSDHAI guidelines. Use of Injectable CAB/RPV LA as Replacement ART in Virally Suppressed Adults. August 2022

WHO FAILS WITH RESISTANCE ON LA CAB + RPV

Parameter	Final Model Or (95% CI), p-value
RPV RAM(s) at baseline	37.24 (8.44->99), p<0.001
Log_2 of *post hoc* Week 8 RPV trough concentration	4.17 (1.59-11.11), p=0.004
Baseline HIV-1 subtype A6/A1	6.59 (1.82-25.26), p=0.005
BMI (kg/m^2) at baseline	1.13 (1.03-1.25), p=0.014

Sensitivity and specificity of at least two baseline factors is optimal

	PPV	NPV	Sensitivity	Specificity
Two or more factors	26%	99.6%	69%	97.5%
Any one factor	<1%	98%	8%	74%

Margolis DA, Schapiro JM, Perno CF et al. Virtual HIV Drug Therapy Glasgow; 5–8 October, 2020.
Cutrell AG, Schapiro JM, Perno CF et al. AIDS 2021.

LA (PRIMA) PRATICA CLINICA

Clinical Infectious Diseases

MAJOR ARTICLE

First Demonstration Project of Long-Acting Injectable Antiretroviral Therapy for Persons With and Without Detectable Human Immunodeficiency Virus (HIV) Viremia in an Urban HIV Clinic

Katerina A. Christopoulos,[1] Janet Grochowski,[1] Francis Mayorga-Munoz,[1] Matthew D. Hickey,[1] Elizabeth Imbert,[1] John D. Szumowski,[1] Samantha Dilworth,[2] Jon Oskarsson,[1] Mary Shiels,[1] Diane Havlir,[1] and Monica Gandhi[1]

[1]Division of HIV, ID, and Global Medicine, University of California–San Francisco, San Francisco, California, USA; and [2]Division of Prevention Science, University of California–San Francisco, San Francisco, California, USA

Characteristics of 39 Patients Initiating Long-Acting Injectable Cabotegravir and Rilpivirine With at Least 2 Follow-up Injections

Characteristic	N (%)
Age, median (IQR, range), years	46 (39–55, 31–68)
Gender	
Cis-gender man	35 (89.7)
Cis-gender woman	3 (7.7)
Transgender woman	1 (2.6)
Race/Ethnicity	
Black	8 (20.5)
Hispanic	10 (25.6)
White	15 (38.5)
Multiracial/Other	6 (15.4)
Housing	
Stable	23 (59.0)
Unstable	13 (33.3)
Homeless	3 (7.7)
Insurance	
Medicare	25 (64.1)
Medicaid	13 (33.3)
Healthy San Francisco (uninsured)	1 (2.6)
Current stimulant use	20 (54.1)
Antiretroviral regimen at referral	
TAF/FTC/BIC	15 (38.5)
TAF/FTC/DRV-c	12 (30.8)
ABC/3TC/DTG	4 (10.3)
Other DTG-containing regimen[a]	4 (10.3)
TDF/3TC/DOR	2 (5.1)
ELV-c containing regimen[b]	2 (5.1)
HIV VL ≥30 copies RNA/mL at time of referral	18 (46.2)
HIV VL ≥30 copies RNA/mL proximal to first injection	15 (38.0)
Log_{10} HIV VL of those with ≥30 copies RNA/mL at first injection, mean (standard deviation)	4.67 (1.16)
CD4 cell count/mm^{3}[c], median (IQR)	
Those with VL ≥30 copies/mL	99 (51–299)
Those with VL <30 copies/mL	732 (364–883)
Attended a primary care visit in each 6-month period of the year prior to first injection	
Those with VL ≥30 copies/mL[d]	14 (93.3)
Those with VL <30 copies/mL	20 (83.3)

- Between June 2021 and April 2022, 51 patient initiated LAI-ART, with 39 receiving at least 2 follow-up injections by database closure (median age, 46 years; 90% cisgender men, 61% non-White, 41% marginally housed, 54% currently using stimulants). Of 24 patients who initiated injections with viral suppression (median CD4 cell count, 706 cells/mm3), 100% (95% confidence interval [CI], 86%–100%) maintained viral suppression. Of 15 patients who initiated injections with detectable viremia (median CD4 cell count, 99 cells/mm3; mean log10 viral load, 4.67; standard deviation, 1.16), 12 (80%; 95% CI, 55%–93%) achieved viral suppression, and the other 3 had a 2-log viral load decline by a median of 22 days.

- In summary, in this small demonstration project, we found that patients with detectable viremia due to challenges adhering to oral ART can be successfully started on CAB/RPV-LA. Our data show early success in suppressing this group of patients on CAB/RPV-LA and in keeping patients with viral suppression suppressed. A longer period of follow-up and a larger cohort, along with other demonstration projects to examine the use of CAB/RPV-LA in hard-to-reach populations and qualitative assessments of acceptability, are needed.

Cabotegravir–rilpivirine treatment initiation in a nonvirologically suppressed patient

Barnett SK et al. AIDS 2022

- We describe a patient who had failed four different traditional oral HIV ART regimens and had no ART resistance who was initiated on a once-monthly injection of cabotegravir–rilpivirine to circumvent poor pill adherence and gastrointestinal concerns.

- A 53-year-old woman with a longstanding history of HIV (diagnosed 2006) and multiple failed ART regimens had been unable to adhere to a daily pill regimen. Genotypes on multiple occasions showed no significant resistance.

- At baseline HIV-RNA 178 000 copies/ml, and CD4 211 cells/ml.

- She was switched to 1 month of oral cabotegravir–rilpivirine with good adherence. She was then prescribed long-acting injectable cabotegravir–rilpivirine administered every 4 weeks to improve adherence and to circumvent any potential gastrointestinal issues that might be affecting absorption/bioavailability. She tolerated the new regimen well.

- After 3 months, the viral load was undetectable, and CD4 count improved to 374 cells/ml. At 6 months, the viral load remained suppressed less than 20 copies/ml with improved CD4 count to 445 cells/ml, and she continued to tolerate the regimen without adverse effects.

LONG-ACTING CABOTEGRAVIR-RILPIVIRINE IN HIGHLY EXPERIENCED PLWHIV: THE ROLE OF DIRECTLY OBSERVED TREATMENT (DOT) IN OVERCOMING BARRIERS TO ADHERENCE

A. Ciccullo et al. Submitted IJAA

Methods

- In this study, we aimed to describe a cohort of PLWHIV switched to long acting CAB+RPV administered at home by a dedicated “home-based care unit”.
- We analyzed data from a cohort of PLWHIV followed in our Infectious Diseases Unit in Rome, assisted via an “home care assistance unit”, with a dedicated teams of doctor and nurses.
- All individuals were switched to the long-acting combination of CAB+RPV in clinical practice, with a every-4-weeks parenteral administration. Decision whether to start or not with a month of oral lead-in was individualized by the physician for each individual.

Variable	N=15
Age (Years), median (IQR)	53 (42-64)
Female sex, n (%)	8 (53.3)
HIV Risk Factor, n (%): - Heterosexual - MSM - IDU	 8 (53.3) 5 (33.3) 2 (13.4)
CDC stage C, n (%)	7 (46.7)
Zenith HIV-RNA (log10 copies/mL), median (IQR)	5.13 (4.34-5.79)
Nadir CD4+ cell count (cell/mm3), median (IQR)	205 (25-294)
Years from HIV diagnosis, median (IQR)	10.9 (5.9-21.1)
Years from ARV initiation, median (IQR)	10.0 (5.0-21.0)
Pre-switch regimen, n (%): - 2NRTI + INI - 3TC+DTG - 2NRTI + DOR	 10 (66.6) 4 (26.7) 1 (6.7)

Results/1

- Historic genotypic analysis was available for 10 (66.6%) individuals, with 3 of them presenting one resistance mutation associated with a potential reduction of rilpivirine susceptivity: 1 V179D, 1 E138A and 1 V106I.
- Three individuals started a month of oral lead-in of CAB+RPV; 2 of them decided to discontinue treatment after the lead-in month.
- At the time of the first parenteral administration, 1/13 (7.7%) had an HIV-RNA of 86 copies/mL, while all other individuals had a HIV-RNA below the threshold of 50 copies/mL; median CD4+ cell count at baseline was 619 cell/mm3 (IQR 239-740) while median CD4/CD8 ratio was 1.06 (IQR 0.44-1.41).
- The individual with a detectable viremia at baseline, a 49 years-old female with a BMI of 21.9 Kg/m2, maintained a persistently detectable HIV-RNA at week 4 (58 copies/mL) and at week 6 (240 copies/mL), before finally achieving a HIV-RNA below 50 copies/mL at week 8. It is worth noting that she had previous genotypic exams that show the absence of resistance mutations in the RT and INI regions.

Results/2

- Two other PLWHIV experienced a single viral blip each, regaining virological suppression at the subsequent visit. At week 8 of follow-up, all analyzed PLWHIV had an HIV-RNA< 50 copies/mL.

- Regarding immunological parameters, we did not find any significant change in absolute CD4+ cell count (p=0.507) or CD4/CD8 ratio (p=0.972) after 8 weeks of follow-up. As to reported side-effects, one individual reported the onset of fever after the first administration, while 2 PLWHIV reported pain at injection site after each administration.

Conclusions

- Our results confirm the efficacy and tolerability of CAB+RPV as a switch strategy in experienced PLWHIV

- The regimen appears to be effective and safe also in non-suppressed PLWHIV and in those with historic RAMs to NNRTIs

- Usefulness of DOT strategy may be in selected difficult-to-treat PLWHIV.

PUNTI per Discussione

- I dati dei trials indicano come PWLH ideali per LA i virosoppressi, senza mutazioni a NNRTI e INI, magri ed aderenti

- Nella pratica clinica le prime esperienze sono su popolazione «difficile», viremici, con scarsa aderenza ed in alcuni casi anche con CD4<200/mmc. Tale popolazione nettamente diversa da quella dei trial clinici, in cui la somministrazione parenterale è una «necessità»

COME PROCEDERE?

Grazie per l’attenzione