

AGORÀ PENITENZIARIA 2018
XIX Congresso Nazionale SIMSPe–ONLUS

Roma, 5 Ottobre 2018

Nuovi paradigmi terapeutici: i Trial Clinici

Giordano Madeddu

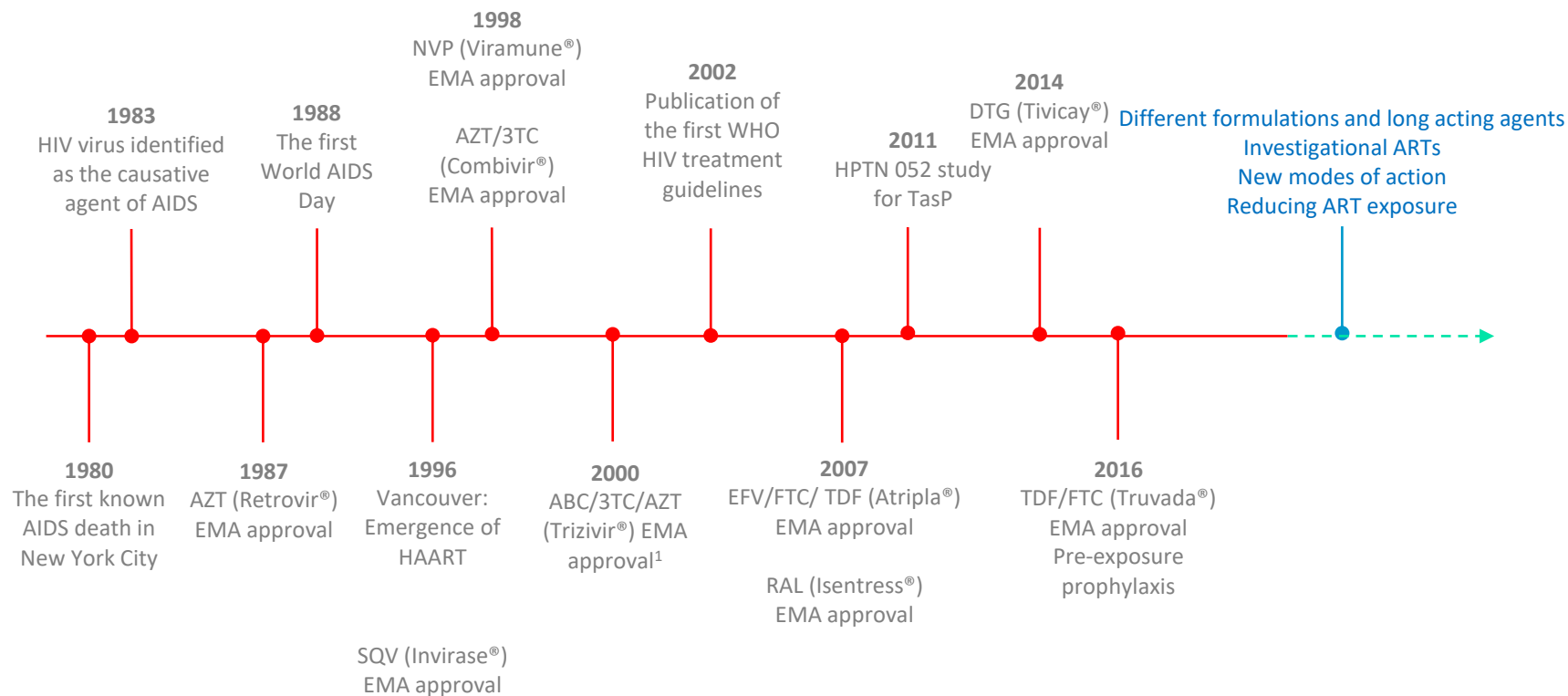


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Disclosure

Prof. Madeddu has received consultancy and/or speakers' fees from Abbott, Bristol Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme and ViiV.

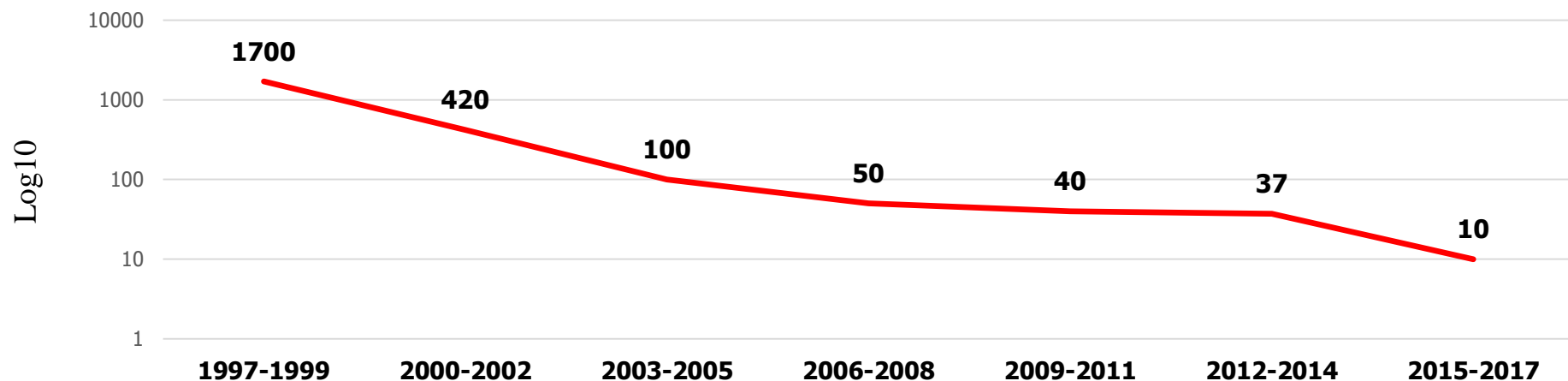
Summary of key HIV milestones



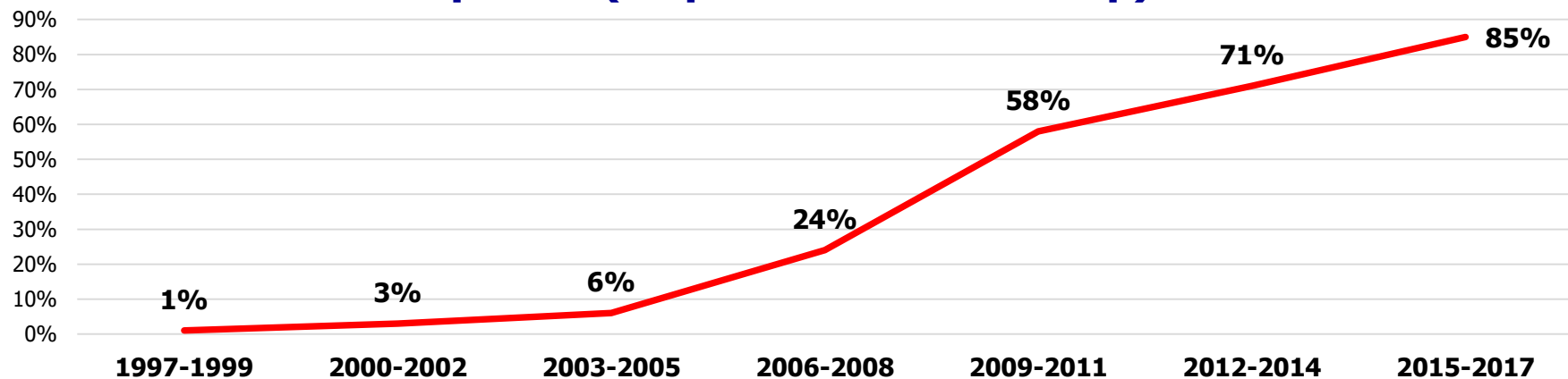
1. Trizivir summary of product characteristics. Last update: April 2016.

ABC, abacavir; ART, antiretroviral therapy; AZT, zidovudine; DTG, dolutegravir; EFV, efavirenz; EMA, European Medicines Agency; FTC, emtricitabine; HAART, highly active antiretroviral therapy; NVP, nevirapine; RAL, raltegravir; SQV, saquinavir; TasP, treatment as prevention; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

Median of HIV-RNA copies/ml per calendar period (all patients in follow-up)



Population VL: proportion of HIV-RNA < 50 per calendar period (all patients in follow-up)





CrossMark

HIV treatment and care among Italian inmates: a one-month point survey

R. Monarca¹, G. Madeddu², R. Ranieri³, S. Carbonara⁴, G. Leo⁵, M. Sardo⁶, F. Choroma⁷, S. Casari⁸, D. Marri⁹, A. A. Muredda², F. A. Nava¹⁰, S. Babudieri^{2*} and SIMSPe-SIMIT Group

Abstract

Background: HIV infection, with an estimated prevalence be between 2 and 50 times those of the general adult population is a major health challenge for prison authorities worldwide. Since no nationwide surveillance system is present in Italy, data on HIV prevalence and treatment in prisons are limited to only a few and small observational studies. We aimed to estimate HIV prevalence and obtain an overview on diagnostic and therapeutic activities concerning HIV infection in the Italian penitentiary system.

Methods: We piloted a multi-centre cross-sectional study investigating the prevalence of HIV infection and assessing HIV-related medical activities in Italian correctional institutions.

Results: A total of 15,675 prisoners from 25 institutions, accounting for approximately one-fourth of the prison inmates in Italy, were included in the study, of whom, 97.7 % were males, 37.1 % foreigners and 27 % had a history of intravenous drug addiction. HIV-tests were available in 42.3 % of the total population, with a known HIV Infection proportion of 5.1 %. In the month prior to the study, 604 of the 1,764 subjects who entered prison were tested for HIV, with a HIV-positive prevalence of 3.3 %. Among the 338 HIV-positive prisoners, 81.4 % were under antiretroviral treatment and 73.5 % showed undetectable HIV-RNA. In 23/338 (6.8 %) a coinfection with HBV and in 189/338 (55.9 %) with HCV was also present. Among the 67 (19.8 %) inmates with HIV who did not receive HIV treatment, 13 (19.5 %) had T-CD4+ count <350 cells/mm³ and 9 (69.2 %) of these had refused the treatment. The majority of the inmates with HIV-infection were on a PI-based (62.5 %) or on NNRTIs-based (24.4 %) regimen. Only a minority of patients received once daily regimens (17.2 %).

Conclusions: Although clinical and therapeutic management of HIV infection remains difficult in Italian prisons, diagnostics, treatment and care were offered to the majority of HIV-infected inmates. Specific programs should be directed towards the prison population and strict cooperation between prison and health institutions is needed to increase HIV treatment.

Keywords: HIV, Patient care, Screening, Antiretroviral treatment, Medication adherence



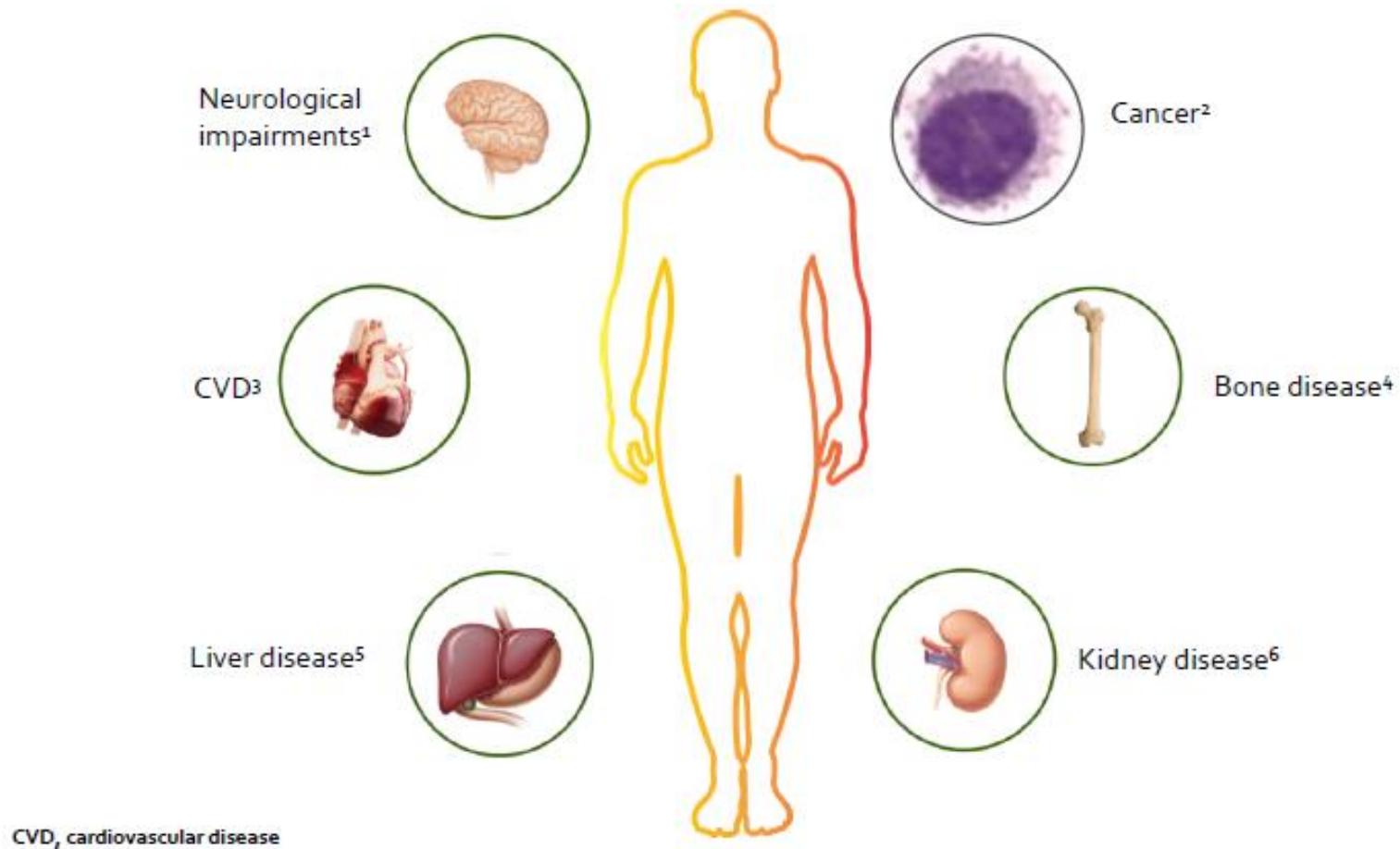
HIV treatment and care among Italian inmates: a one-month point survey

R. Monarca¹, G. Madeddu², R. Ranieri³, S. Carbonara⁴, G. Leo⁵, M. Sardo⁶, F. Choroma⁷, S. Casari⁸, D. Marri⁹, A. A. Muredda², F. A. Nava¹⁰, S. Babudieri^{2*} and SIMSPE-SIMIT Group

Table 2 Antiretroviral regimens received by the 275 HIV-infected inmates on ART

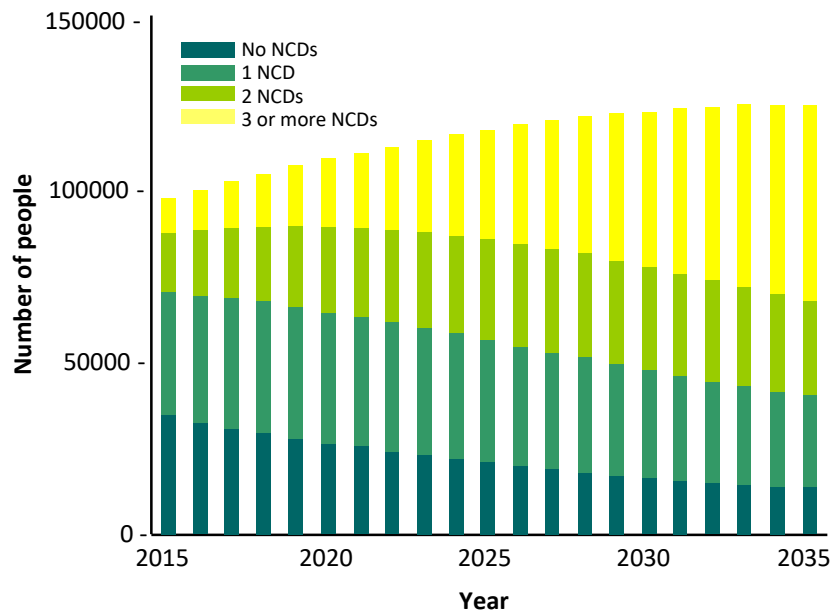
ANTIRETROVIRAL DRUGS	n (%)
Protease inhibitors (PI)	
Atazanavir	88 (32.0 %)
Lopinavir	51 (18.5 %)
Darunavir	23 (8.4 %)
Fosamprenavir	9 (3.3 %)
Saquinavir	1 (0.4)
Total	172 (62.6 %)
Non nucleoside reverse transcriptase inhibitors (NNRTI)	
Efavirenz	50 (18.2 %)
Nevirapine	9 (3.3 %)
Rilpivirine	8 (2.9 %)
Etravirine	5 (1.8 %)
Total	72 (26.2 %)
3 Nucleoside reverse transcriptase inhibitors (NRTI)	
Abacavir-Lamivudine-Zidovudine	6 (2.2 %)
Integrase inhibitors (INI)	
Raltegravir	24 (8.7 %)
CCR5 inhibitors	
Maraviroc	1 (0.4 %)
NRTI backbone	
Tenofovir disoproxilfumarate-emtricitabine	194 (70.5 %)
Abacavir-lamivudine	41 (14.9 %)
Zidovudine-lamivudine	12 (4.4 %)
Other	28 (10.2 %)

HIV infection and ART can have long-term effects on numerous aspects of health



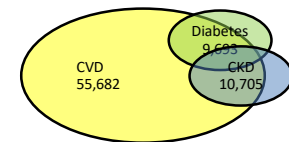
Predicted burden of comorbidities in HIV-positive individuals

Mathematical model to forecast the future clinical burden of ageing for HIV-positive population to Italy between 2015 and 2035

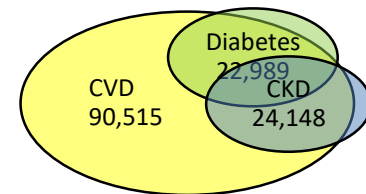


Projected burden of NCDs in HIV+ patients on ART between 2015 and 2035

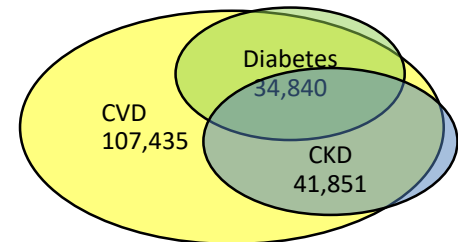
A. 2015



B. 2025



C. 2035



Changes in relative numbers of patients with specific NCDs over time

- Patients on ART with ≥ 3 NCDs will increase from 10% on 2015 to 46% in 2035
- NCD burden increasing with CVD, CKD and diabetes contributing to this. Similar trends to previous forecasts for The Netherlands with the exception of CKD which is expected to contribute to the greater burden in Italy (30% in Italy by 2035 vs 14% in The Netherlands by 2030)

Principles of HIV treatment in prison

- Prisoners bring information with them (education for patient):
 - HIV medications
 - CD4 cells counts and viral load
 - HIV related illness
 - Side effects
- Adherence: build trust and acceptance of ART, reduce institutional barriers to adherence
- Administration of treatment
 - When to start
 - What regimen to use
 - Simplicity, dosing, frequency, side effect profile, drug interactions
 - ARV under direct observation,
 - Modified directly observed therapy (DOT)—significant better results
- Planning for continuity of care from the outset

Challenges to HIV Care and treatment in Prison

- Lack of HIV specialists, integrated delivery systems, community standard practices
- Remote locations
- Continuity of care
- Mistrust and stigma
- Language/cultural barriers
- Restricted formularies
- Confidentiality/privacy

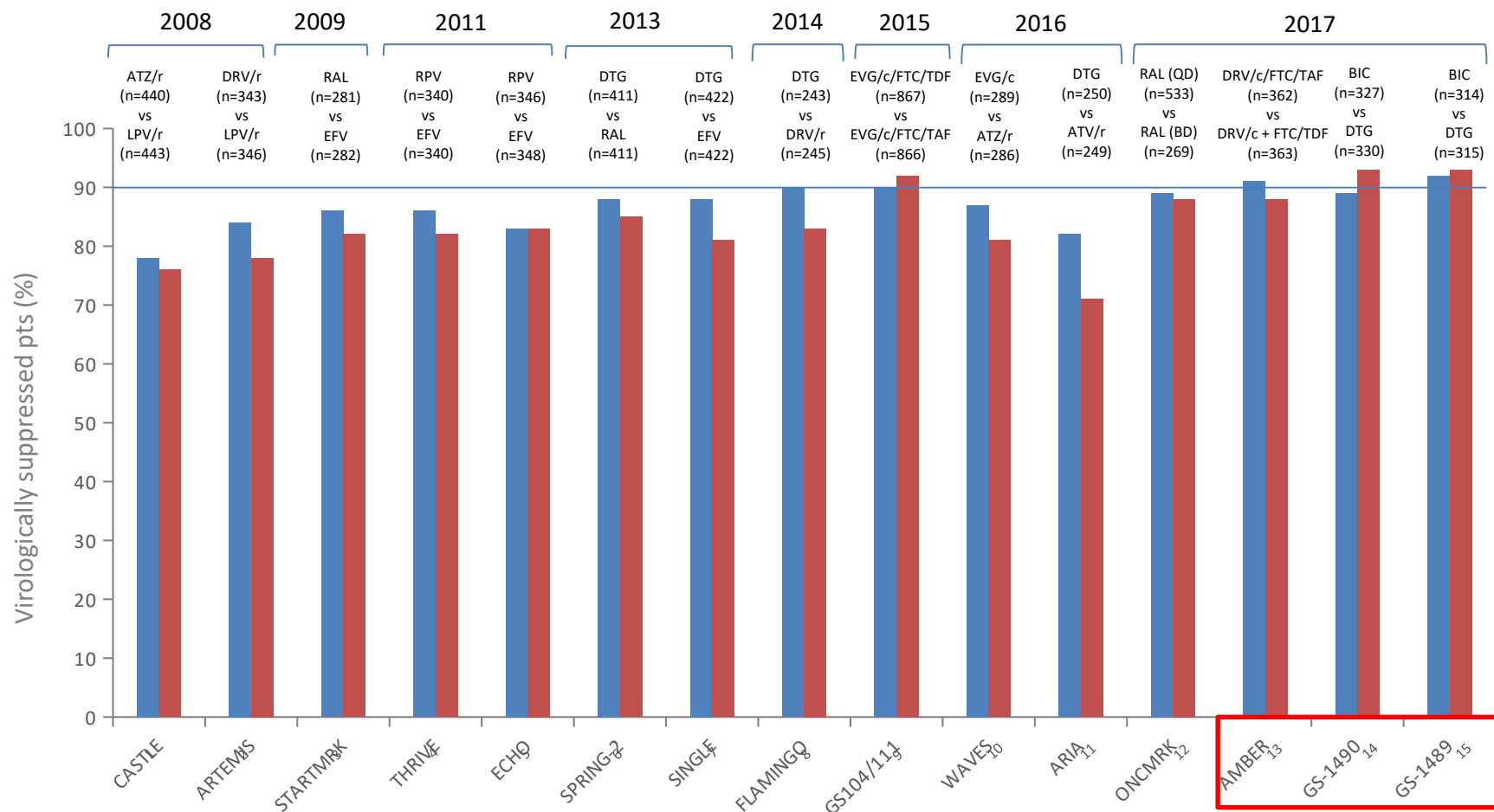
cART in prison

- ✓ Naive patients
- ✓ Suppressed patients

Strategies

- Triple therapy
- LDR

Efficacy outcomes from key triple therapy studies - WK 48



1. Molina JM, et al. *Lancet* 2008;372:646–55; 2. Ortiz R, et al. *AIDS* 2008;22:1389–97; 3. Lennox JL, et al. *Lancet* 2009;374:796–806; 4. Cohen CJ, et al. *Lancet* 2011;378:229–37; 5. Molina JM, et al. *Lancet* 2011;378:238–46; 6. Raffi F, et al. *Lancet* 2013;381:735–43; 7. Walmsley S, et al. *N Engl J Med* 2013;369:1807–18; 8. Clotet B, et al. *Lancet* 2014;383:2222–31; 9. Sax P, et al. *Lancet* 2015;385:2606–15; 10. Squires K, et al. *Lancet HIV* 2016;3:e410–20; 11. Orrell C, et al. *Lancet* 2017;S2352–3018:30095–4; 12. Cahn P, et al. *Lancet HIV* 2017;S2352–3018:30128–5; 13. TBA; 14. Sax PE, et al. *Lancet* 2017;[epub ahead of print]; 15. Gallant J, et al. *Lancet* 2017;[epub ahead of print].

Comparing first line triple therapy ART options in HIV + adults/adolescents 2016/17








GUIDELINES	NRTI BACKBONE				NNRTI			INSTI			PI		
	TAF/ FTC	TDF/ FTC	ABC/ 3TC	AZT/ 3TC	EFV	NVP	RIL	DTG	EVG/c	RAL	ATV/r/c	DRV/r/c	LPV/r
IAS (2016) ¹	Preferred	Alternative/ special situation	Preferred	Not recommended/special situations	Alternative/ special situation	Not recommended/special situations	Alternative/ special situation	Preferred	Preferred	Preferred	Not recommended/special situations	Alternative/ special situation	Not recommended/special situations
DHHS (2017) ²	Preferred	Preferred	Preferred	Not recommended/special situations	Alternative/ special situation	Not recommended/special situations	Alternative/ special situation	Preferred	Preferred	Preferred	Alternative/ special situation	Alternative/ special situation	Not recommended/special situations
EACS (2016) ³	Preferred	Preferred	Preferred	Not recommended/special situations	Alternative/ special situation	Not recommended/special situations	Preferred	Preferred	Preferred	Preferred	Alternative/ special situation	Preferred	Alternative/ special situation
BHIVA ⁴	Preferred	Preferred	Preferred	Not recommended/special situations	Alternative/ special situation	Not recommended/special situations	Preferred	Preferred	Preferred	Preferred	Alternative/ special situation	Preferred	Not recommended/special situations
WHO (2016) ⁵	Not recommended/special situations	Preferred	Not recommended/special situations	Alternative/ special situation	Preferred	Alternative/ special situation	Not recommended/special situations	Alternative/ special situation	Not recommended/special situations	Not recommended/special situations	Not recommended/special situations	Not recommended/special situations	Not recommended/special situations

■ Preferred
 ■ Alternative/ special situation
 ■ Not recommended/special situations

1. Günthard HF *et al.* JAMA 2016;316:191–210; 2. US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. Available from: <https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0>. Accessed October 2017; 3. European AIDS Clinical Society. http://www.eacsociety.org/files/guidelines_8.2-english.pdf. Accessed October 2017; 4. British HIV guidelines. Available from: <http://www.bhiva.org/documents/Guidelines/Treatment/2016/treatment-guidelines-2016-interim-update.pdf>. Accessed October 2017; 5. World Health Organization. http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf. Accessed October 2017; 6. Calmy A. Available from: <http://www.natap.org/2017/IAS/CALMYdraft25juillet.pdf>. Accessed October 2017.

Adapted from Calmy A.⁶

EU-licensed once daily fixed-dose combinations for treatment initiation available in 2017

	ATRIPLA¹	EVIPLERA²	STRIBILD³	TRIUMEQ⁴	GENVOYA⁵	ODEFSEY⁶	SYMITUZA⁷
							
Components	TDF/FTC/EFV	TDF/FTC/RPV	TDF/FTC /EVG/c	DTG/ABC /3TC	TAF/FTC /EVG/c	TAF/FTC/RPV	D/c/F/TAF
Restrictions		Take with food	Take with food	Not with HBV co-infection	Take with food	Take with food	Take with food
Considerations	Premorbid Psychiatric	VL <100,000	Drug-drug interactions	Must be HLAB*5701 - Ve	Drug-drug interactions	VL <100,000	Drug-drug interactions
Approval year	2007	2011	2013	2014	2015	2016	2017

Within next 12 months: BIC/FTC/TAF and DTG/RPV

1. Atripla SmPC. Available from: <https://www.medicines.org.uk/emc/medicine/20505>. Updated May 2017. Accessed October 2017; 2. Eviplera SmPC. Available from: <https://www.medicines.org.uk/emc/medicine/25518>. Updated June 2017. Accessed October 2017; 3. Stribild SmPC. Available from: <https://www.medicines.org.uk/emc/medicine/27810>. Updated June 2017. Accessed October 2018; 4. Triumeq SmPC. Available from: <https://www.medicines.org.uk/emc/medicine/29178>. Updated Jan 2017. Accessed October 2017; 5. Genvoya SmPC. Available from: <https://www.medicines.org.uk/emc/medicine/31225>. Updated Sept 2017. Accessed October 2017; 6. Odefsey SmPC. Available from: <https://www.medicines.org.uk/emc/medicine/32117>. Updated Sept 2017. Accessed October 2017.

B/F/TAF Phase 3 Efficacy through Week 48

Study	Population	Comparator	Efficacy	Resistance
1489 ¹	Naïve	DTG/ABC/3TC	Non-inferior*	0
1490 ²	Naïve	DTG+FTC/TAF	Non-inferior*	0
1844 ³	Suppressed	DTG/ABC/3TC	Non-inferior†	0
1878 ⁴	Suppressed	Boosted PI + 2 NRTIs	Non-inferior†	0‡
1961 ⁵	Suppressed	E/C/F/(TAF or TDF) ATV+RTV + FTC/TDF	Non-inferior†	0**

* For ART-naïve studies: Treatment outcomes [between treatment groups] were similar across subgroups by age, sex, race, baseline viral load, and baseline CD4+ cell count.⁶

† For virologically suppressed studies: Treatment outcomes between treatment groups were similar across subgroups by age, sex, race, and region.^{5,6}

‡ One boosted PI regimen participant on DRV+RTV+ABC/3TC developed ABC mutation L74V

** One E/C/F/TAF participant developed FTC mutation M184M/I/V

**In five Phase 3 trials of 1,440 patients through Week 48
B/F/TAF had non-inferior efficacy with zero emergent resistance**

1. Gallant J, et al. Lancet 2017;390:2063-72.

2. Sax P, et al. Lancet 2017;390:2073-82.

3. Molina JM, et al. CROI 2018. Boston, MA. Oral 22

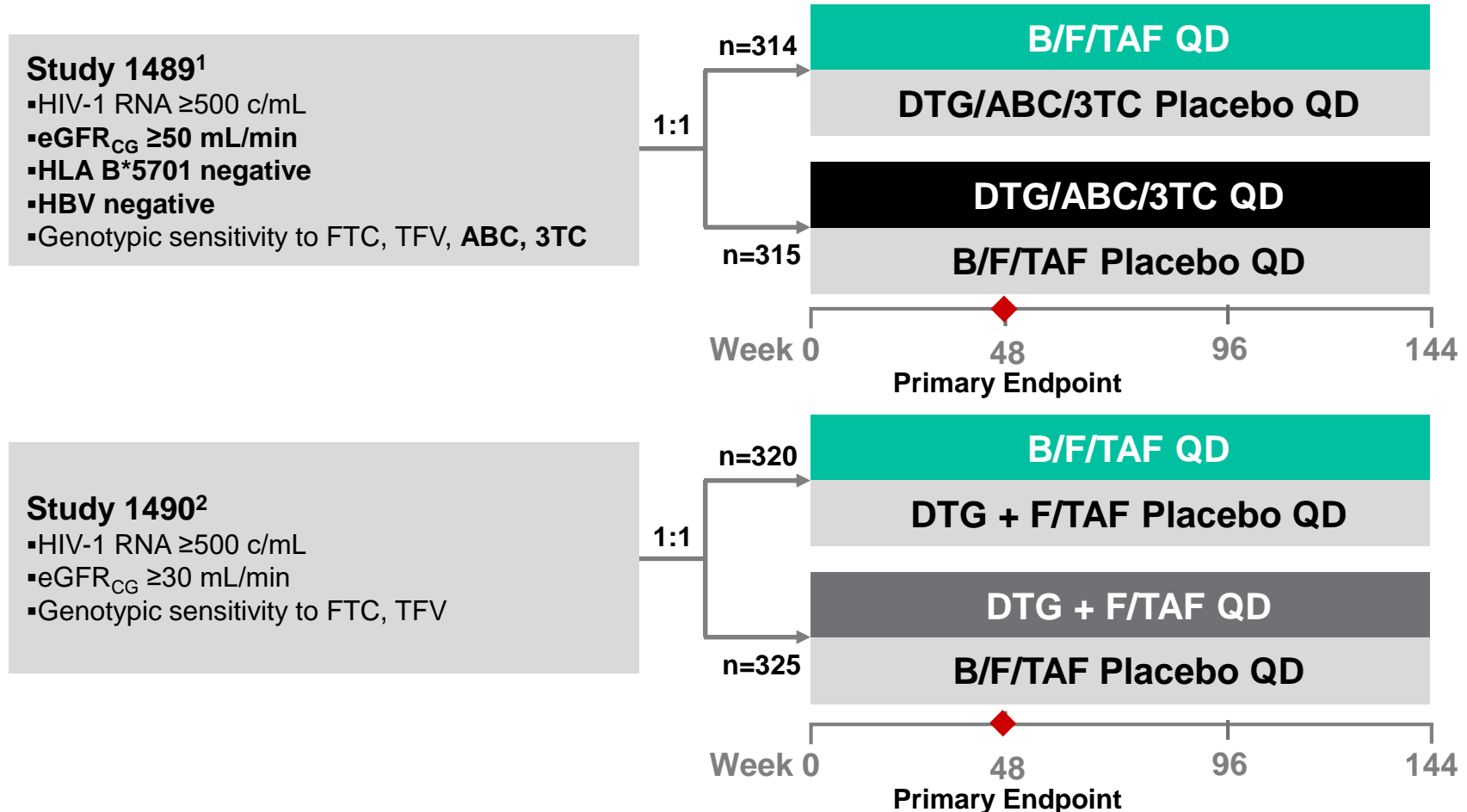
4. Daar E, et al. ID Week 2017. San Diego, CA. Oral LB-4

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

6. Gilead Sciences. Biktarvy US Prescribing Information. February 2018.

Study Designs

B/F/TAF vs DTG-based Regimens



ABC, abacavir; eGFR_{CG}, estimated glomerular filtration rate by Cockcroft Gault; FTC, emtricitabine; HBV, hepatitis B virus; HLA, human leukocyte antigen; TFV, tenofovir; 3TC, lamivudine. **ABC/3TC requirements are marked with bold.**

1. Gallant J, et al. Lancet 2017;390:2063-72.

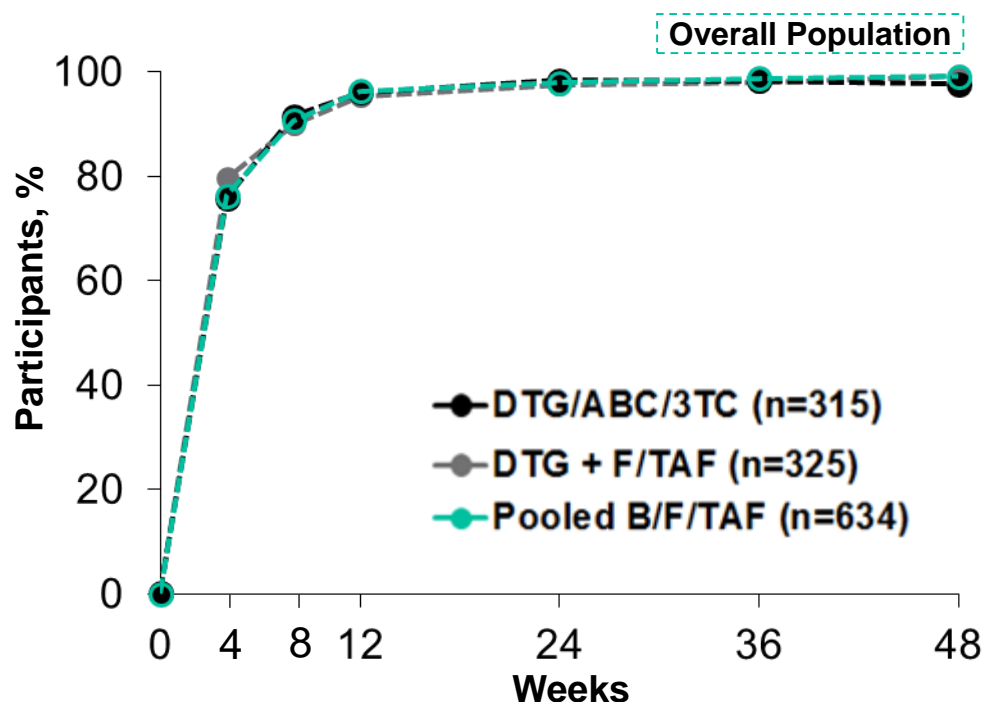
2. Sax P, et al. Lancet 2017;390:2073-82.

3. Podzamczar D, et al. AIDS 2018. Amsterdam, NL. Poster THPEB038

Virologic Response by Visit

Overall Population

HIV-1 RNA <50 c/mL Over 48 Weeks (Missing = Excluded)

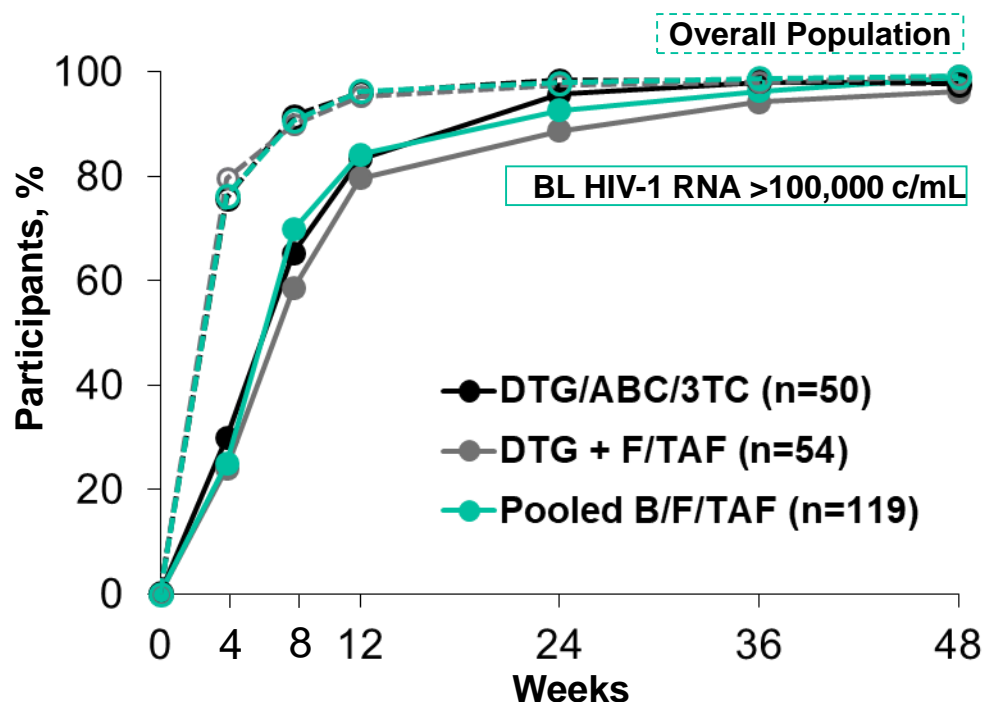


- Majority of B/F/TAF participants achieved rapid suppression to HIV-1 RNA <50 c/mL
 - By Week 4, mean 3.3 log₁₀ decline in HIV-1 RNA
- B/F/TAF virologic response was similar to the DTG-based regimens

Virologic Response by Visit

Baseline HIV-1 RNA >100,000 copies/mL*

HIV-1 RNA <50 c/mL Over 48 Weeks (Missing = Excluded)

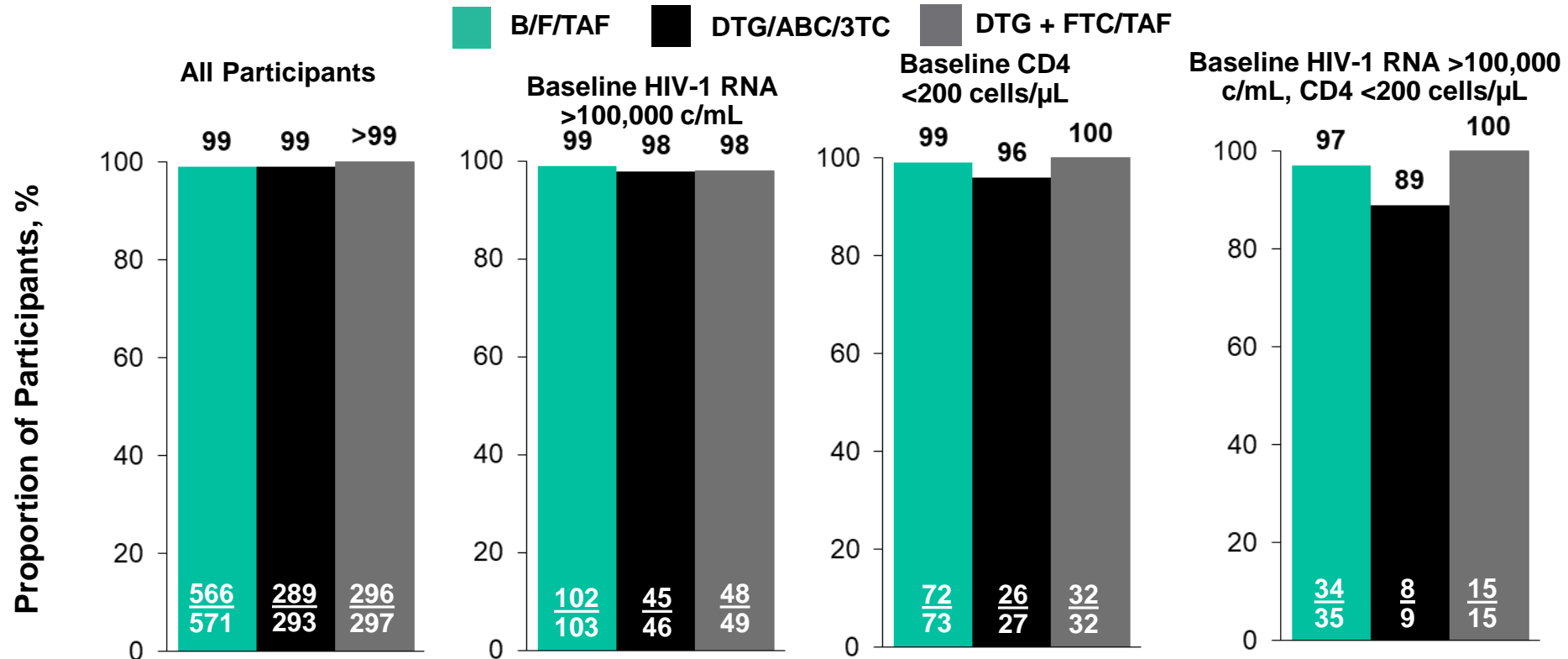


- **For participants with high baseline HIV-1 RNA >100,000 c/mL**
 - Rapid, similar HIV-1 RNA declines throughout 48 weeks for B/F/TAF and DTG regimens

* Samples sizes are data on file

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

Pooled Per-Protocol Analysis



- No participants discontinued due to lack of efficacy and developed emergent resistance

Virologic suppression rates were similarly high for B/F/TAF and DTG-containing regimens regardless of high viral load, low CD4 counts, or both

Summary of HIV Symptom Index Bothersome Symptoms Favoring B/F/TAF over DTG-based Regimens*

	Study 1489 Treatment-naïve				Study 1844 Virologically suppressed			
	Week [†]			Longitudinal Model [‡]	Week [†]			Longitudinal Model [‡]
	4	12	48		4	12	48	
<i>Nausea/vomiting</i>	✓	✓		✓		✓	✓	✓
<i>Loss of appetite</i>		✓		✓		✓		✓
<i>Difficulty sleeping</i>		✓	✓			✓		✓
<i>Fatigue / loss of energy</i>	✓	✓	✓	✓	✓			
<i>Dizzy / lightheadedness</i>	✓		✓		✓			✓
<i>Sad/down/depressed</i>					✓		✓	✓
<i>Nervous/anxious</i>					✓	✓	✓	✓

✓ = Statistically significant ($p < 0.05$), based on the adjusted logistic regression model, favoring the B/F/TAF group over the DTG/ABC/3TC group*

Across studies of treatment-naïve and virologically suppressed adults, bothersome symptoms were reported by fewer participants on B/F/TAF than those on DTG/ABC/3TC

*Hair loss at Week 4 in Study 1844 was the only PRO that favored DTG/ABC/3TC

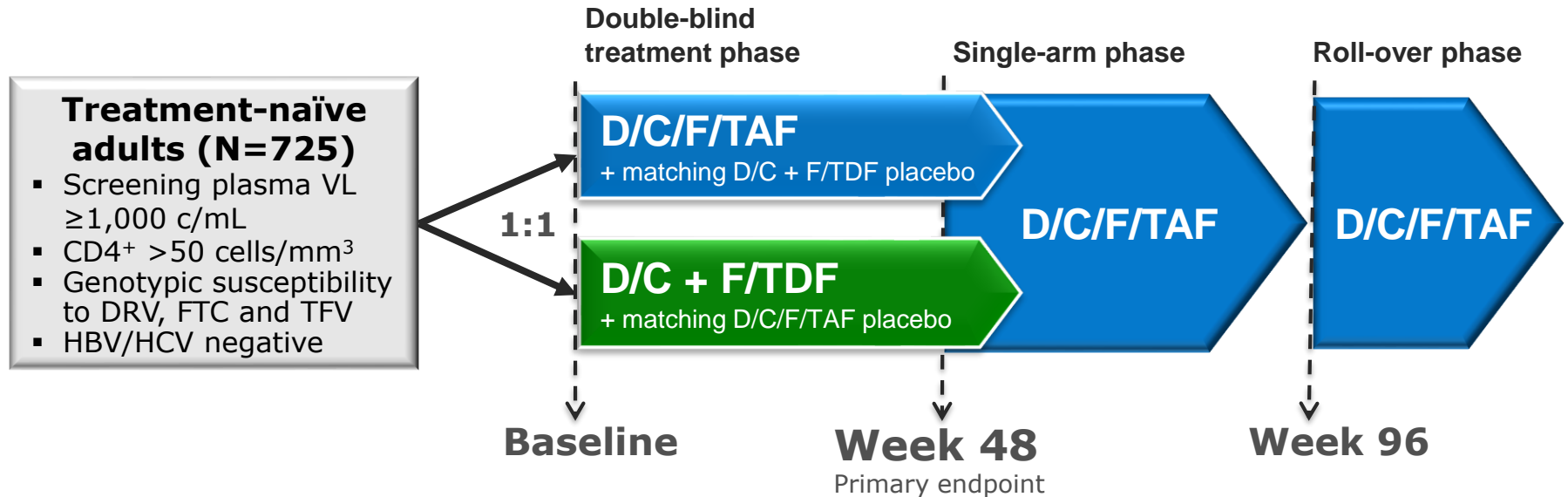
[†] Multivariate regression model controlled for age, sex, race, baseline HIV Symptom Index score, VACS Index, history of serious mental illness, baseline SF36 physical and mental scores, and years since diagnosis (for study 1844 only).

[‡] Longitudinal modeling was performed using generalized mixed-effects models to show symptom patterns over each of the four study visits.

Wohl D, et al. The Patient 2018. <https://doi.org/10.1007/s40271-018-0322-8>

Wohl D, et al. AIDS 2018. Amsterdam, NL. Poster TUPEB148

AMBER: Phase 3, Randomised, Double-blind, International,* Multicentre Trial



Primary objective: Assess non-inferiority of D/C/F/TAF vs D/C + F/TDF by proportion of patients with VL <50 c/mL at 48 weeks (NI margin 10%; FDA-Snapshot algorithm)[†]

Randomisation stratified by screening VL $\leq / > 100,000$ c/mL and CD4⁺ $< / \geq 200$ cells/mm³

*121 sites in USA, Canada, Belgium, France, Germany, Italy, Poland, Russia, Spain, UK

[†]Lower limit of 95% CI of stratified Mantel-Haenszel difference between D/C/F/TAF and control >-10%

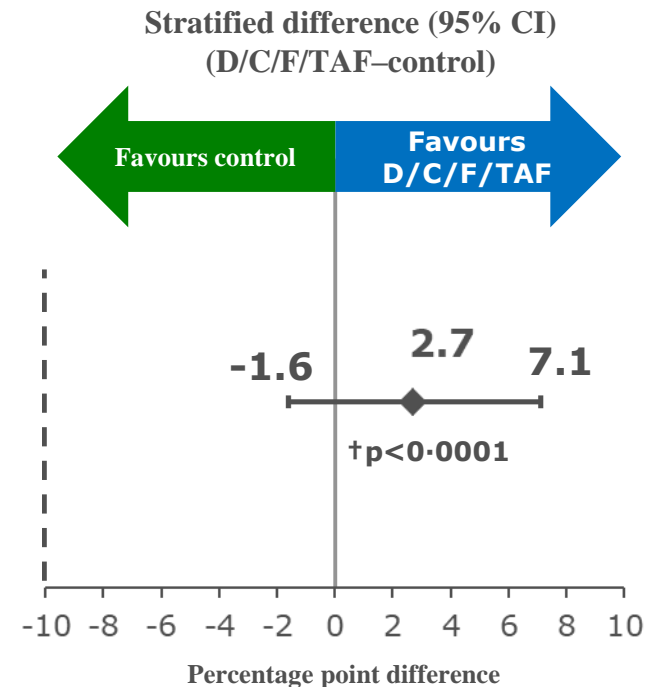
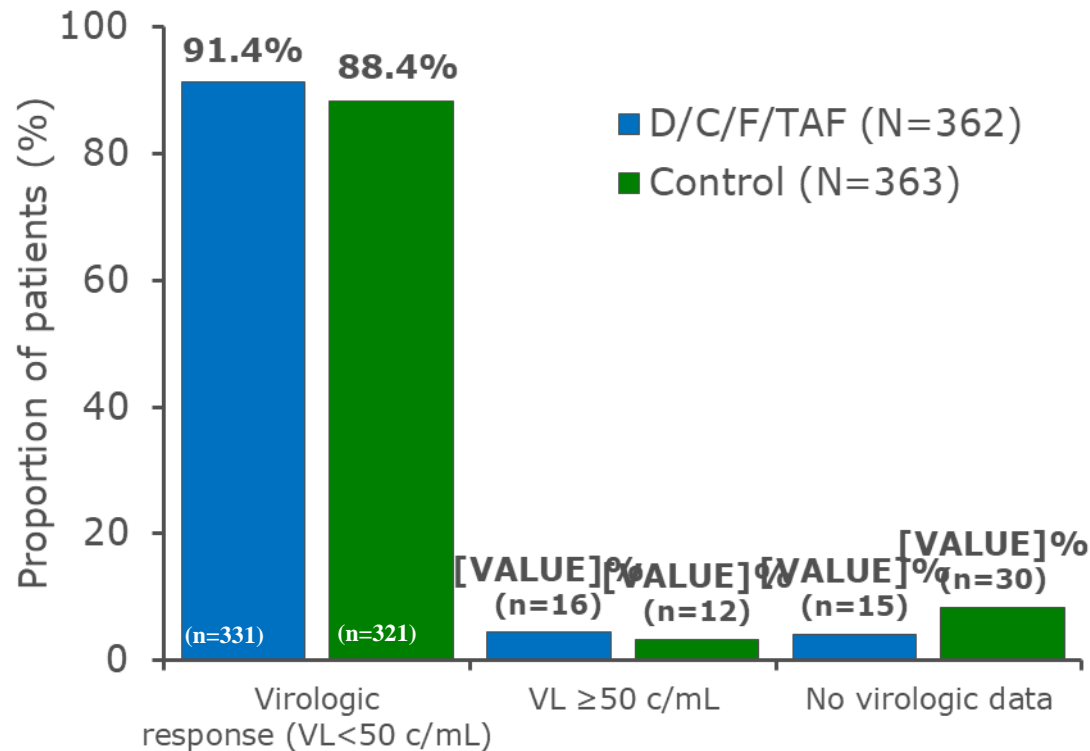
AMBER: Baseline Characteristics

	D/C/F/TAF N=362	Control N=363	Total N=725
Median (IQR) age, years	34 (27–42)	34 (27–42)	34 (27–42)
Male, n (%)	318 (87.8)	322 (88.7)	640 (88.3)
Race, n (%)			
White	300 (82.9)	300 (82.6)	600 (82.8)
Black/African-American	40 (11.0)	40 (11.0)	80 (11.0)
Other races	22 (6.1)	23 (6.3)	45 (6.2)
Median (IQR) log ₁₀ VL, c/mL	4.4 (4.0–4.8)	4.6 (4.2–4.9)	4.5 (4.1–4.9)
VL ≥100,000 c/mL, n (%)	60 (16.6)	70 (19.3)	130 (17.9)
Median (IQR) CD4 ⁺ count, cells/mm ³	461.5 (342–617)	440.0 (325–594)	453.0 (333–601)
CD4 ⁺ count <200 cells/mm ³	22 (6.1)	29 (8.0)	51 (7.0)
Median (IQR) eGFR _{cr} mL/min (Cockcroft-Gault)	119 (105–135)	118 (103–138)	119 (104–136.5)
Genotype at screening	N=361	N=362	N=723
≥1 NNRTI RAMs	55 (15.2)	63 (17.4)	118 (16.3)
≥1 NRTI RAMs	18 (5.0)	16 (4.4)	34 (4.7)
≥1 primary PI RAMs	7 (1.9)	8 (2.2)	15 (2.1)

Virologic Outcome at Week 48 (FDA Snapshot; VL<50 c/mL) (ITT)

D/C/F/TAF non-inferior to control

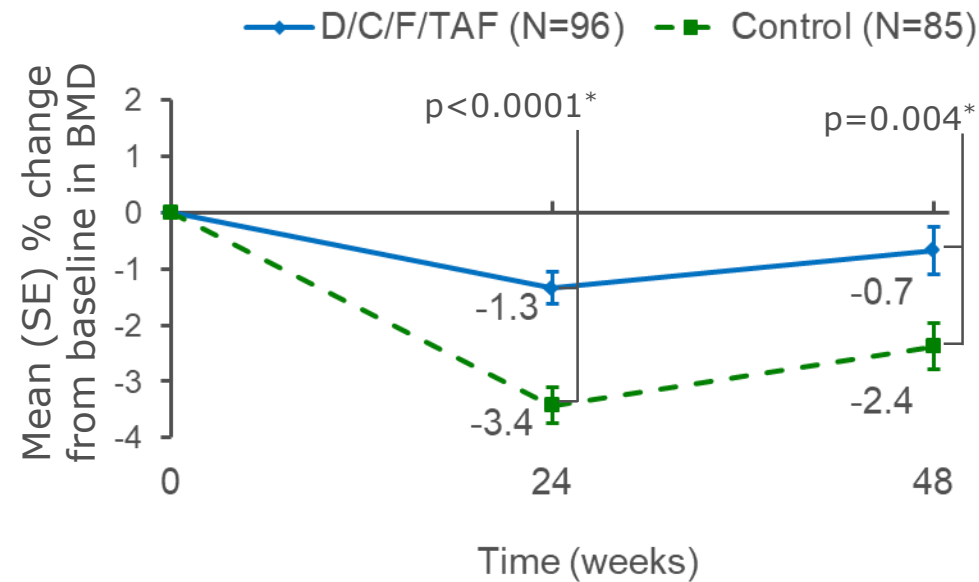
Lower bound 95% CI > -10%



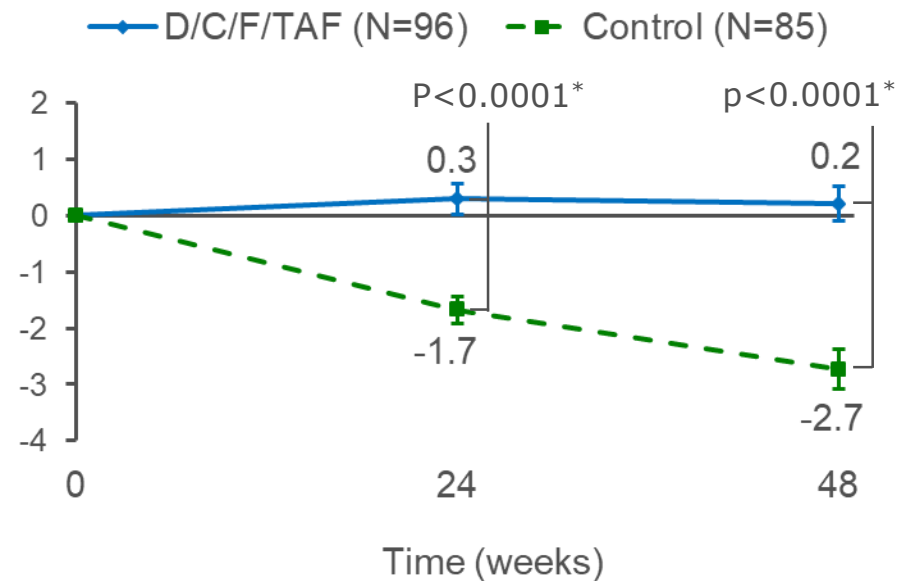
†p-value for non-inferiority at 10% NI margin

Mean % Changes in BMD Through 48 Weeks (DEXA Sub-study)

Spine



Hip

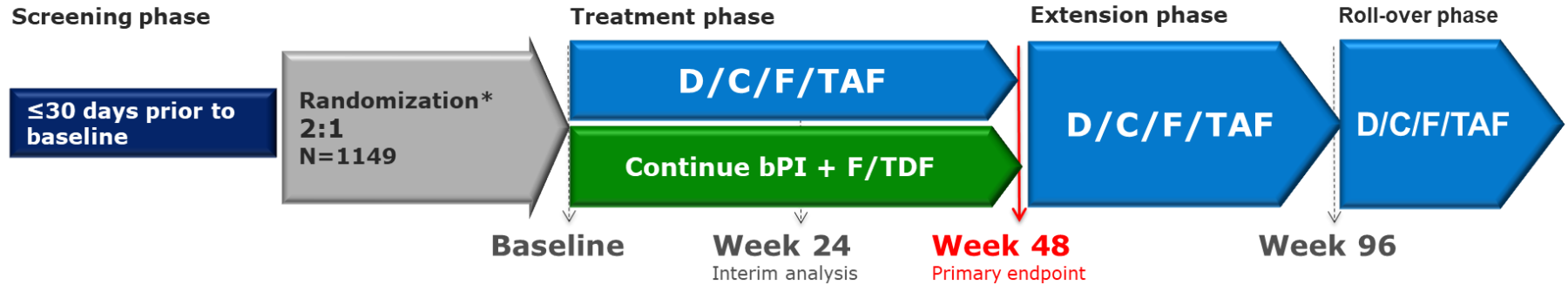


	D/C/F/TAF	Control
≥3% decrease	27.1%	41.2%
≥3% increase	12.5%	4.7%

	D/C/F/TAF	Control
≥3% decrease	12.5%	44.7%
≥3% increase	12.5%	2.4%

*p value for difference estimated using ANCOVA, including treatment as a factor and baseline BMD as a covariate

EMERALD: Phase III, Randomized, Open-label, Multicenter Trial



Objective: Assess efficacy (non-inferiority) and safety of switching to D/C/F/TAF vs continuing bPI + F/TDF regimens in virologically suppressed HIV-1-infected adults at Week 48

Key inclusion criteria:

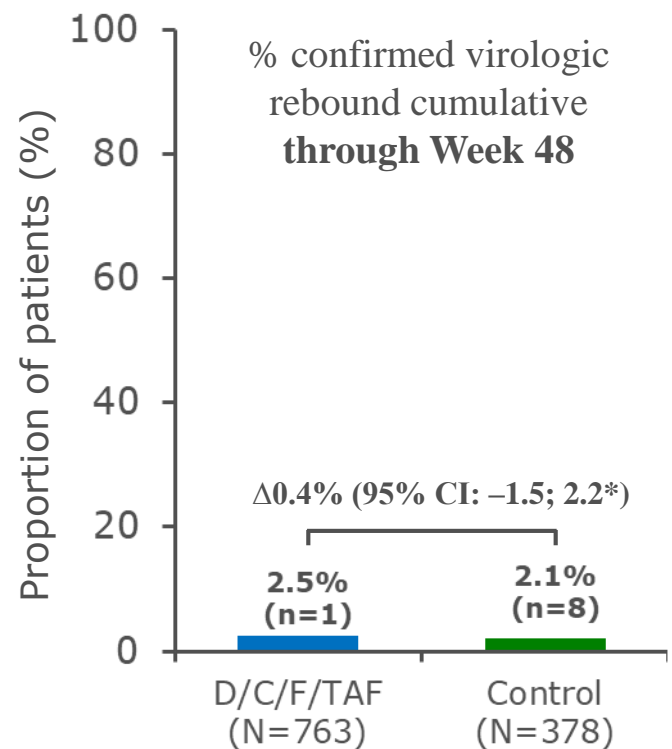
- On a stable bPI + F/TDF regimen for at least 6 months
- Viral load (VL) <50 c/mL for ≥2 months before screening; one 50≤VL<200 c/mL within 12 months prior to screening allowed
- Creatinine clearance (by Cockcroft-Gault) ≥50 mL/min
- Previous ART virologic failure (VF) allowed
- Absence of history of VF on DRV, and if historical genotype available, absence of DRV RAMs[†]

Stratified by bPI (protease inhibitor boosted with low-dose ritonavir or COBI) at screening; [†]DRV RAMs: V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V (IAS-USA)

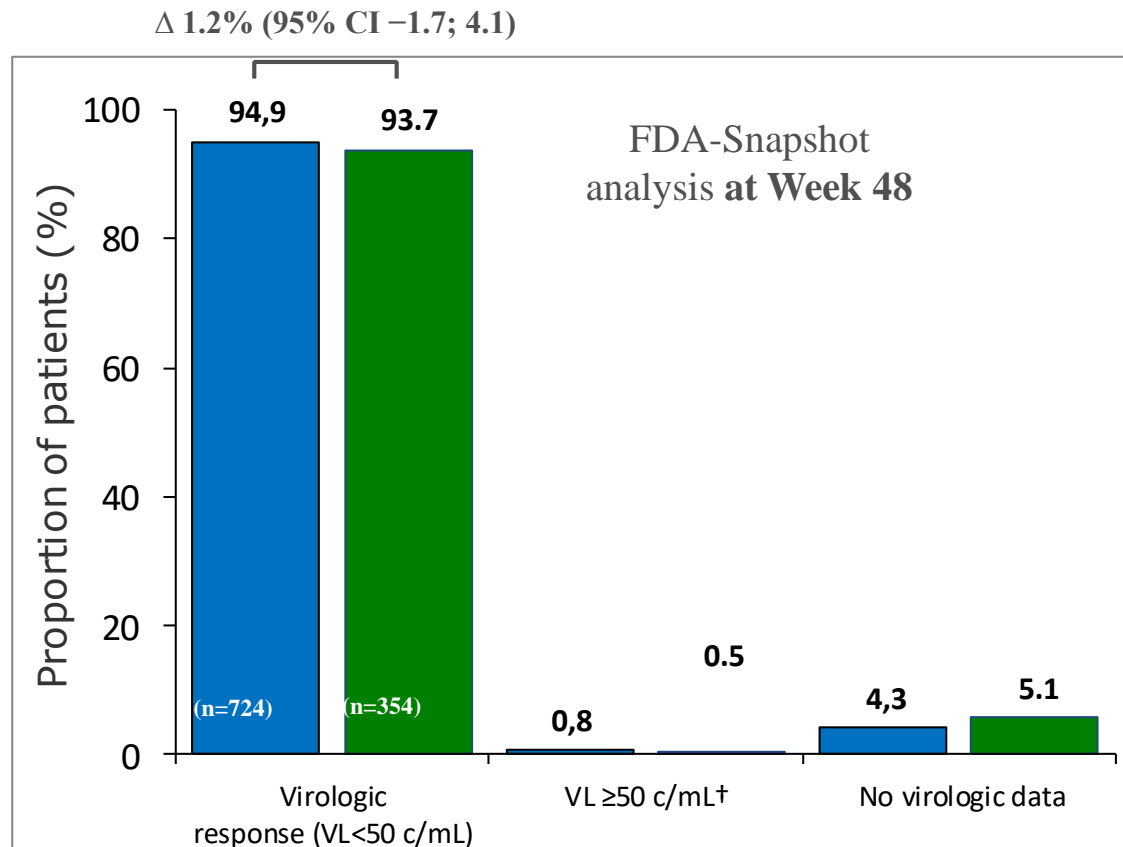
Baseline Demographics and Disease Characteristics

	D/C/F/TA F QD N=763	Control N=378	Total N=1141
Median (range) age, years	46 (19–75)	45 (20–78)	46 (19–78)
Female, n (%)	140 (18.3)	65 (17.2)	205 (18.0)
Race, n (%)			
White	573 (75.1)	282 (74.6)	855 (74.9)
Black	155 (20.3)	82 (21.7)	237 (20.8)
Other	35 (4.6)	14 (3.7)	49 (4.3)
Median (range) years since diagnosis	9.3 (0.6–35.0)	8.9 (0.6–32.6)	9.3 (0.6–35.0)
Median (range) CD4 ⁺ count, cells/mm ³	630 (111–1921)	624 (131–1764)	628 (111–1921)
Used ≥1 ARV prior to screening regimen, n (%)	447 (58.6)	217 (57.4)	664 (58.2)
Prior VF, n (%)	116 (15.2)	53 (14.1)	169 (14.8)
Boosted PI at screening, n (%)			
DRV	537 (70.4)	266 (70.4)	803 (70.4)
ATV	167 (21.9)	82 (21.7)	249 (21.8)
LPV	59 (7.7)	30 (7.9)	89 (7.8)
COBI, n (%)	104 (13.6)	65 (17.2)	169 (14.8)

Week 48 Efficacy



*Upper bound 95% CI <4.0% (p<0.0001)



[†]Last VL in W48 window ≥ 50 c/mL, or discontinuation for efficacy reasons, or premature discontinuations (\neq efficacy/AE/death), with last (single) VL ≥ 50 c/mL

- No discontinuations for efficacy reasons
- Most rebounders (12/19 D/C/F/TAF and 4/8 control) resuppressed (<50 c/mL) at Week 48

Resistance Analysis Through Week 48

- Post-baseline genotyping performed in rebounders with VL ≥ 400 c/mL at failure, at later time points or at discontinuation
- Post-baseline genotypes available for:
 - 1 rebounder (D/C/F/TAF) and 3 rebounders (control)
- **No DRV, primary PI, TFV or FTC RAMs observed**

Adverse Events Regardless of Causality Through Week 48

Incidence, n (%)	D/C/F/TAF QD N=763	Control N=378
≥1 AE, any grade	625 (81.9)	311 (82.3)
≥1 grade 3–4 AE	52 (6.8)	31 (8.2)
≥1 serious AE	35 (4.6)	18 (4.8)
≥1 AE leading to permanent discontinuation	11 (1.4)	5 (1.3)
Discontinuations due to renal AEs	1 (0.1) ^a	2 (0.5) ^b
Deaths	0	0
Most common AEs (≥5% both arms)		
Nasopharyngitis	81 (10.6)	39 (10.3)
Upper respiratory tract infection	81 (10.6)	39 (10.3)
Back pain	54 (7.1)	21 (5.6)
Vitamin D deficiency	50 (6.6)	27 (7.1)
Osteopenia	38 (5.0)	21 (5.6)

^a D/C/F/TAF: one worsening of a pre-existing chronic kidney disease (Grade 2, non-serious);

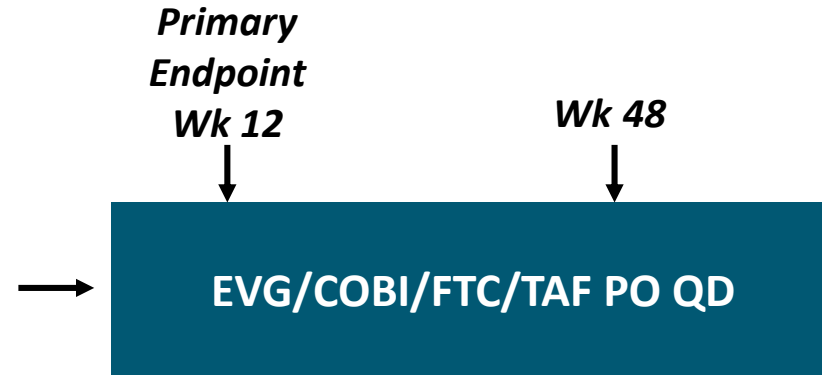
^b Control: one toxic nephropathy (Grade 4, non-serious) and one renal tubular disorder (Grade 1)

Study 1824: Switch to EVG/COBI/FTC/TAF in Virologically Suppressed Adults With M184V/I

- Ongoing, international, multicenter, open-label, single-arm phase IIb pilot study

HIV-infected adults with HIV-1 RNA < 50 copies/mL for

≥ 6 mos on TDF/FTC or ABC/3TC + third agent*; M184V and/or M184I on historical genotypic resistance test[†]; no previous VF on PI- or INSTI-based regimen; eGFR ≥ 30 mL/min (N = 37)



*At baseline, 54% of patients receiving PI, 32% INSTI, 11% NNRTI.

[†]51% (19/37) of patients also had evidence of baseline NNRTI resistance.

- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 12 by PVR, defined as
 - No confirmed VF (HIV-1 RNA ≥ 50 copies/mL on 2 consecutive visits) before Wk 12
 - No premature d/c with last available HIV-1 RNA ≥ 50 copies/mL
 - EVG/COBI/FTC/TAF d/c before Wk 12 for reasons other than viral rebound considered to have PVR

Study 1824: Efficacy and Safety

- HIV-1 RNA < 50 copies/mL
 - Wk 12: 37/37 (100%)
 - Wk 24: 37/37 (100%)
- No evidence of virologic failure or treatment-emergent resistance at Wks 12 or 24
- Single viral blips in 2 patients: HIV-1 RNA 69 or 93 copies/mL, respectively

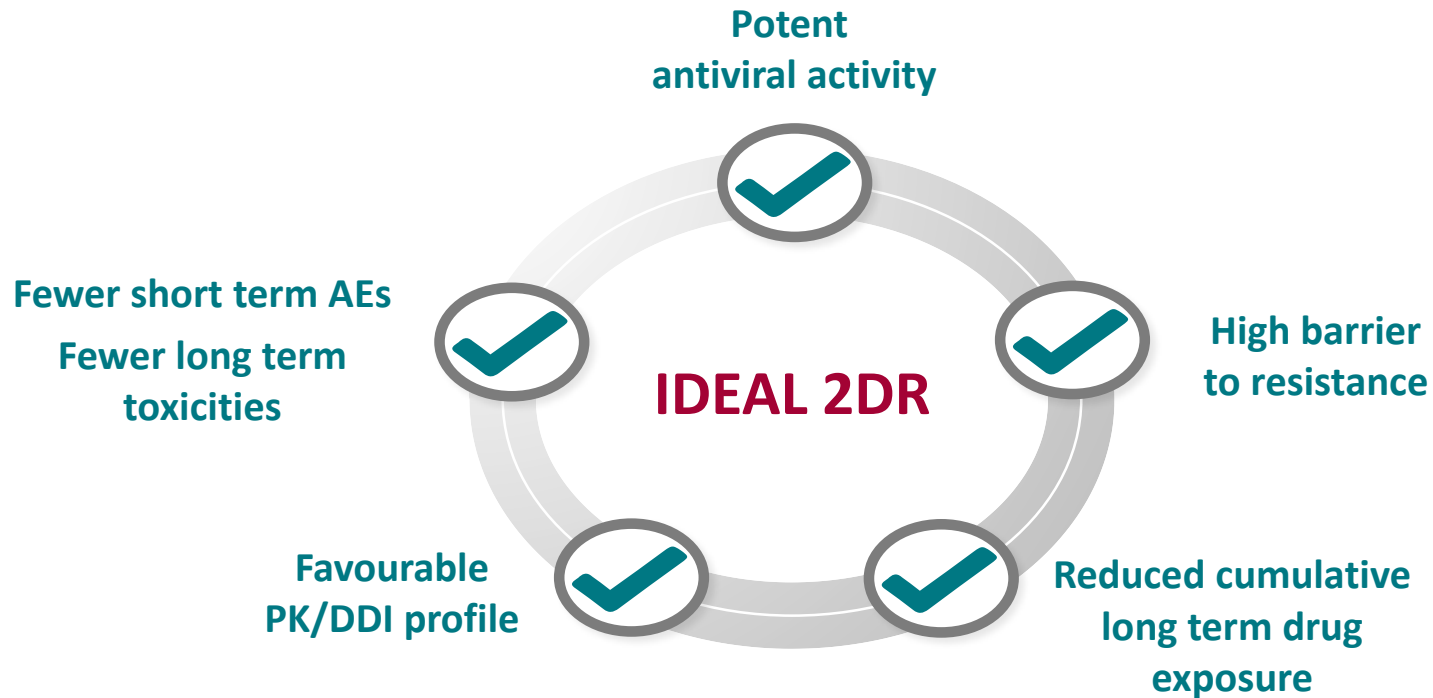
AE, n (%)	E/C/F/TA F (n = 37)
Any AE	29 (78)
■ Drug related	8 (22) [†]
Grade 2-4 AE	15 (40)
■ Drug related	5 (14)
Grade 3/4 AE*	5 (14)
AE leading to premature study drug d/c	1 (3)
■ Drug related	1 (3)
Serious AE*	4 (11) [‡]

*None deemed related to study drugs.

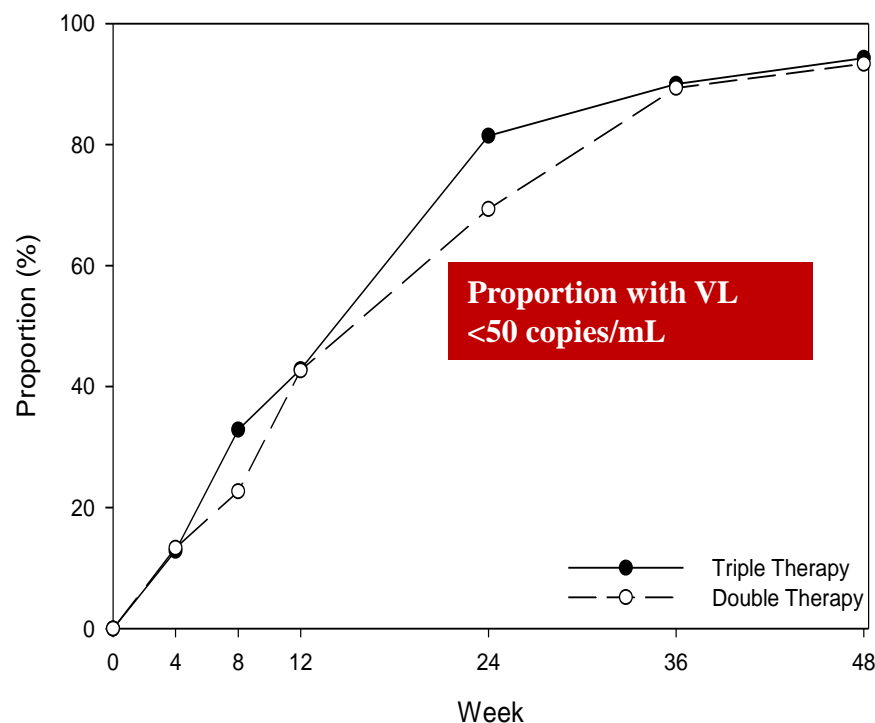
[†]Asthenia, fatigue, headache, each n = 2; diarrhea, skin burning sensation, HTN, muscle spasms, each n = 1.

[‡]Tonsillar carcinoma, pleural adenocarcinoma, proteinuria, acute kidney injury/renal failure, each n = 1.

What makes an ideal 2DR?



ANDES – Dual (DRV +RTV+3TC) vs Triple Therapy – 48 weeks



% <50 at W 48	TT n (%)	2DC n (%)	Difference (95% CI)
ITT snapshot (n=145)	66 (94%)	70 (93%)	-1.0% (-7.5-5.6%)
ITT snapshot VL >100,000 (n=35)	12 (92%)	20 (91%)	-1.4% (-17.2-14.4%)
Observed (n=140)	66 (99%)	70 (100%)	1.5% (-0.9-3.9%)

- Most frequent G2-4 AEs gastrointestinal (TT: 14%; DT: 7%; p:0.17) & rash (TT 7%, DT 8%; p:0.95)
- Lab abnormalities similar except total cholesterol (change to W48: TT: 4%; DT: 19%; p: 0.01); LDL & TG showed non-significant trend favouring TT
- AE discontinuations rare & similar; no treatment-related SAEs or deaths

Non-Inferior Efficacy of Dolutegravir (DTG) Plus Lamivudine (3TC) vs DTG Plus Tenofovir/Emtricitabine (TDF/FTC) Fixed-Dose Combination in Antiretroviral Treatment–Naive Adults With HIV-1 Infection—Week 48 Results From the GEMINI Studies

P. Cahn,¹ J. Sierra Madero,² J. Arribas,³ A. Antinori,⁴ R. Ortiz,⁵ A. Clarke,⁶ C.-C. Hung,⁷ J. Rockstroh,⁸ P.-M. Girard,⁹ C. Man,¹⁰ J. Sievers,¹¹ A. Currie,¹² M. Underwood,¹⁰ A. Tenorio,¹⁰ K. Pappa,¹⁰ B. Wynne,¹⁰ M. Gartland,¹⁰ M. Aboud,¹¹ K. Smith¹⁰

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Orlando, FL, USA; ⁶Royal Sussex County Hospital, Brighton, UK;

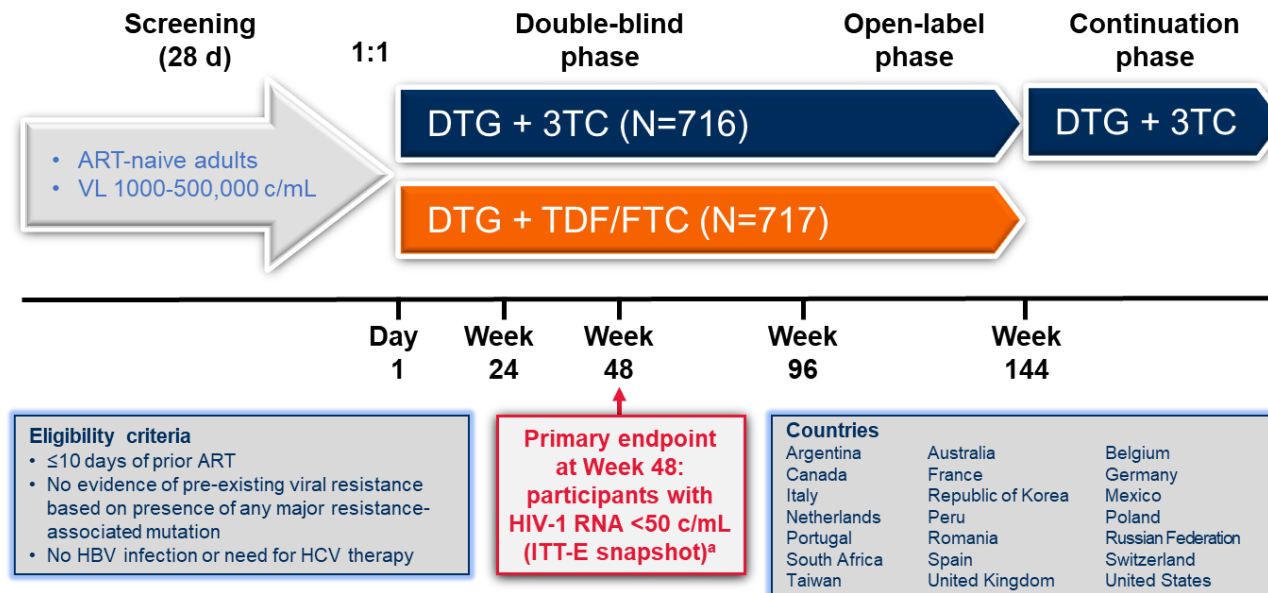
⁷National Taiwan University Hospital, Taipei, Taiwan, Province of China; ⁸Rheinische Friedrich-Wilhelms Universität, Bonn, Germany; ⁹Hôpital Saint Antoine, Paris, France; ¹⁰ViiV Healthcare, Research Triangle Park, NC, USA;

¹¹ViiV Healthcare, Brentford, UK; ¹²GlaxoSmithKline, Stockley Park, UK

GEMINI-1 and -2 Phase III Study

Study Design

Identically designed, randomized, double-blind, parallel-group, multicenter, noninferiority studies



Baseline stratification factors: plasma HIV-1 RNA (≤100,000 c/mL vs >100,000 c/mL) CD4+ cell count (≤200 cells/mm³ vs >200 cells/mm³).

^a–10% noninferiority margin for individual studies.

GEMINI-1 and -2 Phase III Study

Demographic and Baseline Characteristics for the Pooled GEMINI-1 and -2 Population

Characteristic	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Age, median (range), y	32.0 (18-72)	33.0 (18-70)
≥50 y, n (%)	65 (9)	80 (11)
Female, n (%)	113 (16)	98 (14)
Race, n (%)		
African American/African heritage	99 (14)	76 (11)
Asian	71 (10)	72 (10)
White	480 (67)	497 (69)
Other	66 (9)	72 (10)
Ethnicity, n (%)		
Hispanic or Latino	215 (30)	232 (32)
Not Hispanic or Latino	501 (70)	485 (68)
HIV-1 RNA, median (range), log₁₀ c/mL	4.43 (1.59-6.27)	4.46 (2.11-6.37)
≤100,000	576 (80)	564 (79)
>100,000 ^a	140 (20)	153 (21)
CD4+ cell count, median (range), cells/mm³	427.0 (19-1399)	438.0 (19-1497)
>200	653 (91)	662 (92)
≤200	63 (9)	55 (8)

^a2% of participants in each arm had baseline HIV-1 RNA >500,000 c/mL

GEMINI-1 and -2 Phase III Study

Confirmed Virologic Withdrawals Through Week 48: ITT-E Population

- Low rates of virologic withdrawals were observed at Week 48

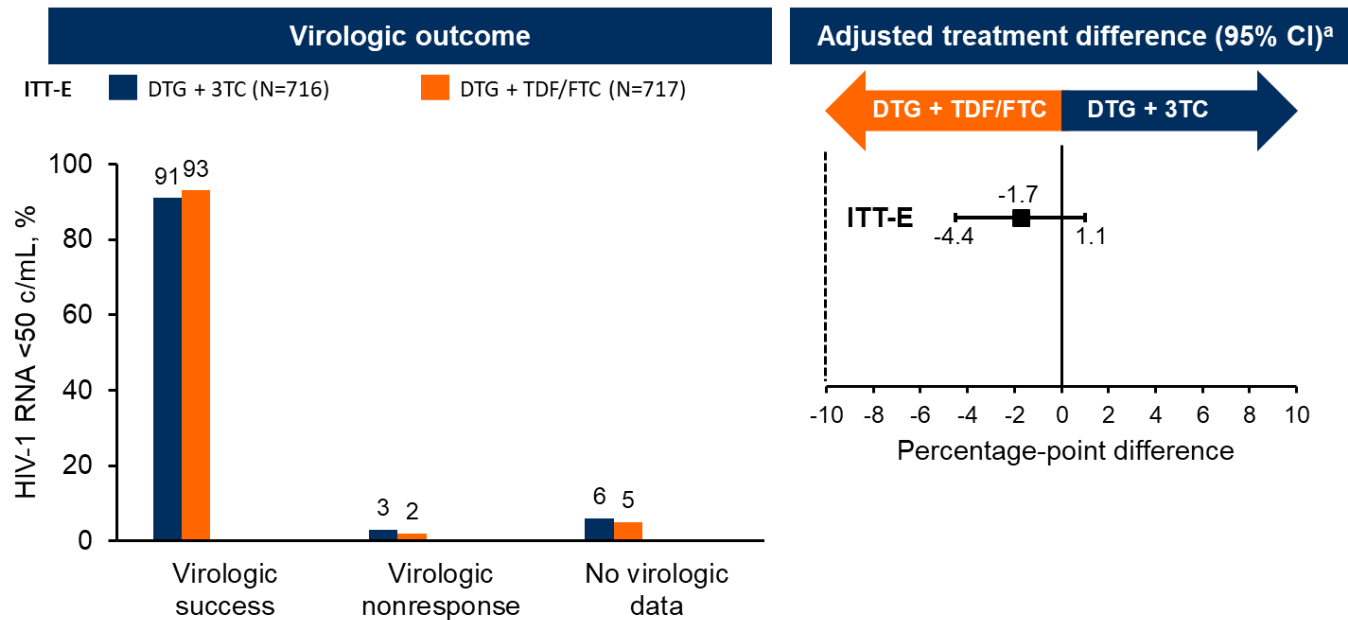
Variable, n (%)	GEMINI 1		GEMINI 2		Pooled	
	DTG + 3TC (N=356)	DTG + TDF/FTC (N=358)	DTG + 3TC (N=360)	DTG + TDF/FTC (N=359)	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
CVW	4 (1)	2 (<1)	2 (<1)	2 (<1)	6 (<1)	4 (<1)
Treatment-emergent resistance	0	0	0	0	0	0

- No treatment-emergent INSTI mutations or NRTI mutations were observed among participants who met CVW (confirmed virologic failure) criteria

- Confirmed virologic withdrawal criteria is defined as a second and consecutive HIV-1 RNA value meeting virologic non-response or rebound.
 - Virologic non-response is defined as either a decrease in plasma HIV-1 RNA of less than 1 log₁₀ c/mL by Week 12 with subsequent confirmation unless plasma HIV-1 RNA is <200 c/mL, or confirmed plasma HIV-1 RNA levels ≥200 c/mL on or after Week 24.
 - Virologic rebound is defined as confirmed rebound in plasma HIV-1 RNA levels to ≥200 c/mL after prior confirmed suppression to <200 c/mL.

GEMINI-1 and -2 Phase III Study

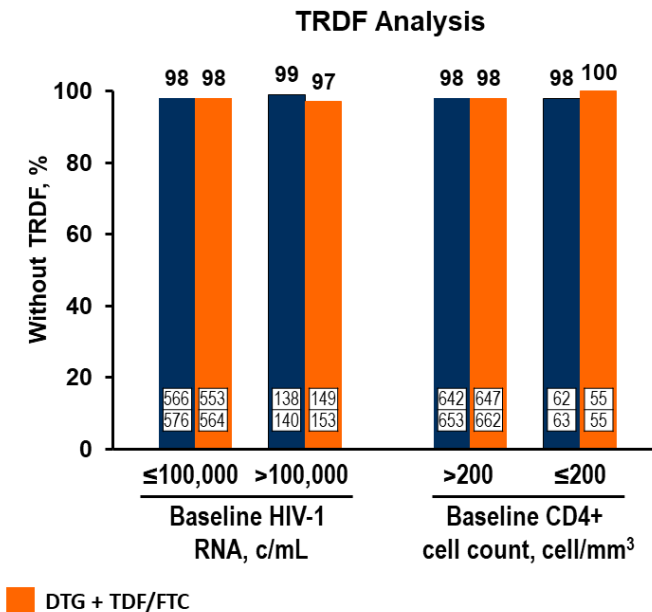
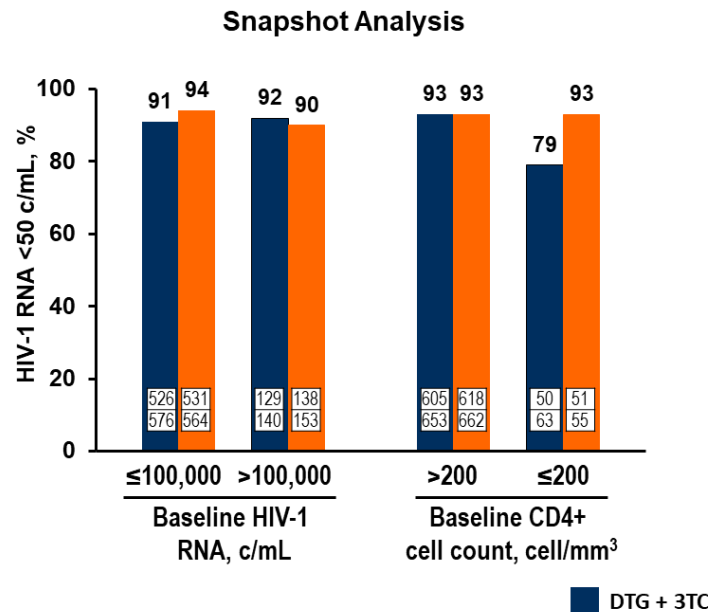
Pooled Snapshot Outcomes at Week 48: ITT-E Population



^aBased on Cochran-Mantel-Haenszel stratified analysis adjusting for the following baseline stratification factors: plasma HIV-1 RNA ($\leq 100,000$ c/mL vs $>100,000$ c/mL), CD4+ cell count (≤ 200 cells/mm³ vs >200 cells/mm³), and study (GEMINI-1 vs GEMINI-2).

GEMINI-1 and -2 Phase III Study

Pooled Outcomes at Week 48 Stratified by Baseline HIV-1 RNA and CD4+ Cell Count: Snapshot and TRDF Analysis



2% (14 and 15 respectively) of participants in each arm had baseline HIV-1 RNA >500,000 c/mL
 n=18 participants had baseline HIV-1 RNA>400,000 (n=26 had HIV-1 RNA>400,000 in B/F/TAF naïve studies)

- 2% of participants in each arm had baseline HIV-1 RNA >500,000 c/mL
- Treatment related discontinuation = failure (TRDF) population accounts for confirmed virologic withdrawal (CVW), withdrawal due to lack of efficacy, withdrawal due to treatment-related AE, and participants who met protocol-defined stopping criteria

Cahn et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

Durable Suppression 2 Years After Switch to Dolutegravir + Rilpivirine 2-Drug Regimen: SWORD-1 and SWORD-2 Studies

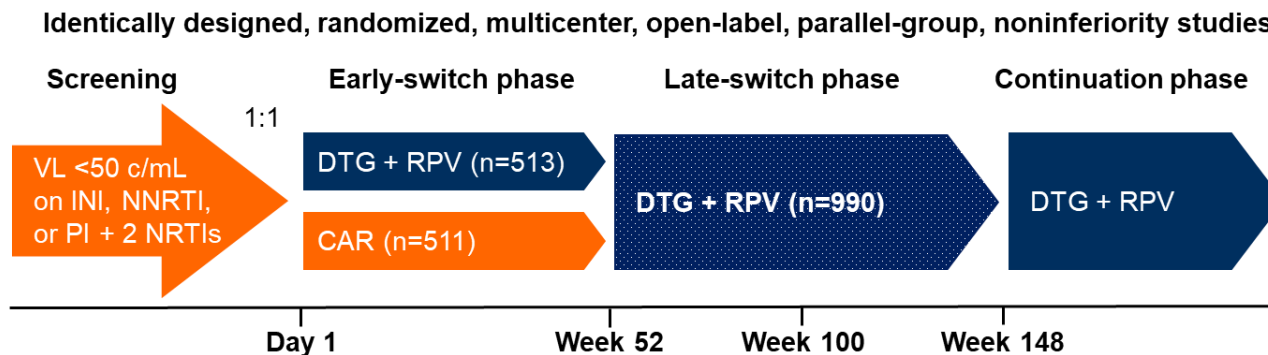
Aboud M,¹ Orkin C,² Podzamczar D,³ Bogner J,⁴ Baker D,⁵ Khuong-Josses M-A,⁶ Parks D,⁷ Angelis K,⁸ Kahl L,¹ Blair E,⁹ Underwood M,⁹ Wynne B,¹⁰ Vandermeulen K,¹¹ Gartland M,⁹ Smith K⁹

¹ViiV Healthcare, Brentford, UK; ²Barts Health NHS Trust, London, UK; ³Hospital Universitari de Bellvitge, Barcelona, Spain; ⁴Hospital of the University of Munich, Munich, Germany; ⁵East Sydney Doctors, Darlinghurst, Sydney, Australia; ⁶CHG - Hôpital Delafontaine, Saint Denis Cedex, France; ⁷Central West Clinical Research, St Louis, MO, USA; ⁸GlaxoSmithKline, Uxbridge, UK; ⁹ViiV Healthcare, Research Triangle Park, NC, USA; ¹⁰ViiV Healthcare, Collegeville, PA, USA; ¹¹Janssen Pharmaceutica NV, Beerse, Belgium

SWORD 1 and 2 – 100 weeks

SWORD-1 and SWORD-2 Phase III - Study Design and population disposition

- SWORD-1 and SWORD-2 were identically designed, randomized, multicenter, open-label, parallel-group, noninferiority phase III studies
 - A full description of the study design, including eligibility criteria and endpoints, has been previously reported^a

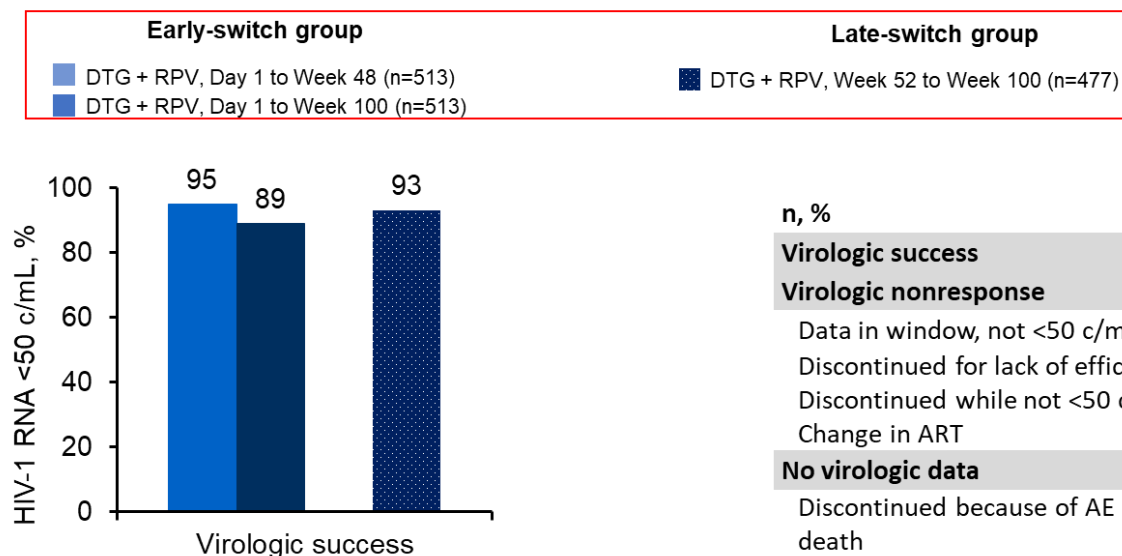
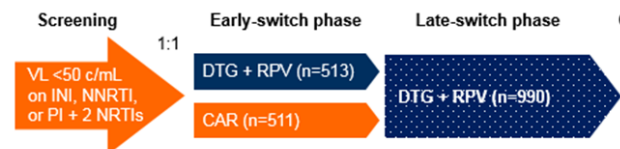


^aLlibre et al. *Lancet*. 2018;391:839-849.

SWORD 1 and 2 – 96 weeks

Virologic Efficacy

- Through 100 weeks of treatment, DTG + RPV continued to be efficacious in the early-switch group
 - Virologic efficacy in the late-switch group at Week 100 was similar to that of the early-switch group at Week 48



n, %	Early-switch group		Late-switch group
	DTG + RPV Week 48 (n=513)	DTG + RPV Week 100 (n= 513)	DTG + RPV Week 100 (n= 477)
Virologic success	486 (95)	456 (89)	444 (93)
Virologic nonresponse	3 (<1)	13 (3)	10 (2)
Data in window, not <50 c/mL	0	5 (<1)	3 (<1)
Discontinued for lack of efficacy	2 (<1)	7 (1)	3 (<1)
Discontinued while not <50 c/mL	1 (<1)	1 (<1)	0
Change in ART	0	0	4 (<1)
No virologic data	24 (5)	44 (9)	23 (5)
Discontinued because of AE or death	17 (3)	27 (5)	11 (2)
Discontinued for other reasons ^a	7 (1)	17 (3)	9 (2)
Missing data during window but on study	0	0	3 (<1)

^aOther reasons for discontinuation while treated with DTG + RPV were lost to follow-up, n=3; protocol deviation, n=5 (prohibited medication use, n=3; pregnancy, n=2); withdrawal of consent, n=18 (participant relocated, n=5; travel burden, n=2; other, n=9); and investigator discretion, n=2.

SWORD 1 and 2 – 100 weeks

NNRTI Resistance-Associated Mutations

- Through Week 100, there was a low number of confirmed virologic withdrawals across study populations **(1%; 10/990)**
- CVWs with resistance-associated treatment-emergent mutations were low across both groups and detected in 3 participants, all receiving DTG + RPV **(0.3%; 3/990)**
 - In all 3 participants, at least 1 NNRTI resistance-associated mutation was detected

Week of failure	Previous regimen	Viral loads, copies/mL ^b	Resistance mutations ^a		Fold change
			Baseline (GenoSure ^c)	Confirmed virologic withdrawal	
Week 24	EFV/TDF/FTC	<u>88</u> ; 466	NNRTI: none INSTI: G193E	NNRTI: none INSTI: G193E	DTG, 1.02
Week 36	EFV/TDF/FTC	<u>1,059,771</u> ; 1018; <50	NNRTI: none INSTI: none	NNRTI: K101K/E INSTI: none	RPV, 1.21
Week 64 ^d	DTG/ABC/3TC	<u>833</u> ; 1174; <50	NNRTI: none INSTI: N155N/H, G163G/R	INSTI resistance test failed	————
Week 76 ^d	ATV, ABC/3TC	<u>79</u> ; 162; 217	————	Test not performed ^e	————
Week 88	DTG/ABC/3TC	<u>278</u> ; 2571; 55	NNRTI: none INSTI: none	NNRTI: E138E/A INSTI: none	RPV, 1.61 DTG, 0.72
Week 88	RPV/TDF/FTC	<u>147</u> ; 289	————	Test not performed ^e	————
Week 100	EFV/TDF/FTC	<u>651</u> ; 1105; 300	NNRTI: K101E, E138A INSTI: G193E	NNRTI: K101E, E138A, M230M/L INSTI resistance test failed	RPV, 31
Week 100	ATV, RTV, TDF/FTC	<u>280</u> ; 225; 154	NNRTI: none INSTI: none	NNRTI: none INSTI: none	————

^aShading represents participants with treatment-emergent NNRTI resistance-associated mutations.

^bUnderlined value denotes viral load when participant met virologic withdrawal.

^cHIV-1 baseline resistance testing was performed on integrated HIV-1 proviral DNA using GenoSure Archive[®] assay (Monogram Biosciences, South San Francisco, CA). On-study resistance testing used standard plasma-based genotypic and phenotypic resistance testing.

^dParticipants in the late-switch group.

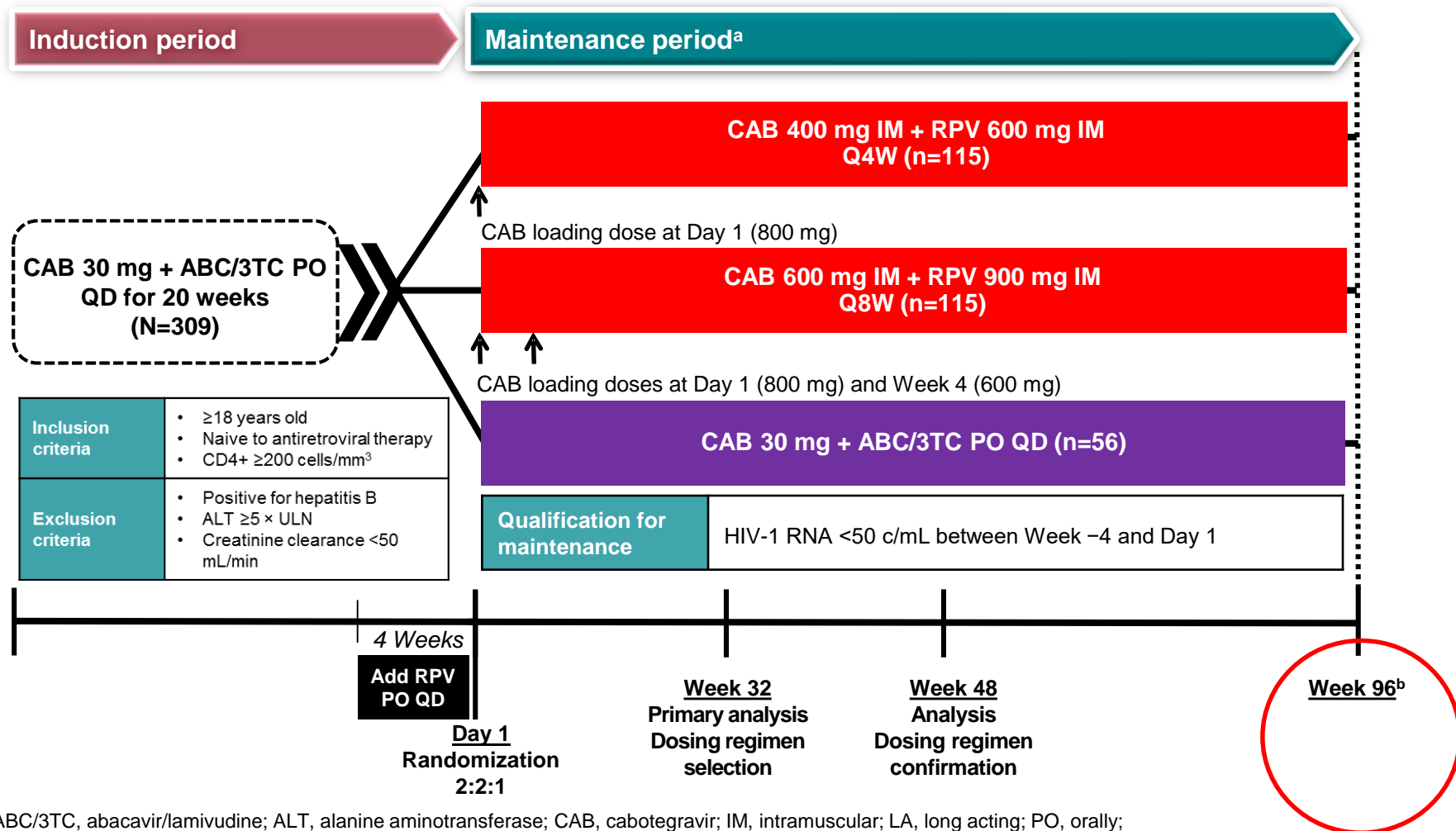
^eResistance testing not performed because of low viral load.

SWORD 1 and 2 – 100 weeks

Conclusions

- Durable efficacy: high level of virologic suppression maintained through 100 weeks in the early-switch group
- Reproducible outcomes: 93% efficacy in the late-switch group (48 weeks after switching to DTG + RPV), consistent with 95% efficacy in the early-switch group at Week 48
- No CVWs with INSTI mutations; CVWs with NNRTI mutations rare (0.3%; 3/990 through Week 100), with minimal impact on future treatment options
- Safety profile of late-switch group similar to early-switch group 48 weeks post-switch
- Switching to DTG + RPV had favorable effect on renal tubular function as evidenced by changes from baseline in retinol-binding protein/creatinine ratio and beta-2 microglobulin/creatinine ratio
- Data through Week 100 support efficacy and safety of switching to once-daily DTG + RPV for patients with HIV-1 on stable, suppressive 3- or 4-drug ART

LATTE-2 Study Design



ABC/3TC, abacavir/lamivudine; ALT, alanine aminotransferase; CAB, cabotegravir; IM, intramuscular; LA, long acting; PO, orally; QD, once daily; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; ULN, upper limit of normal.

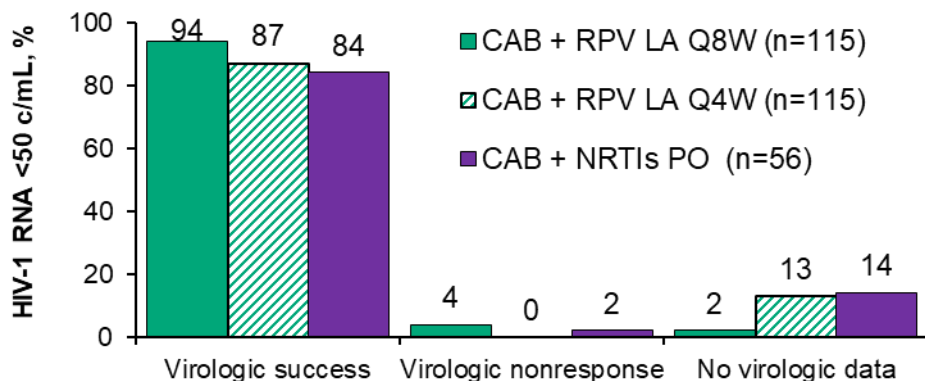
^aSubjects who withdrew after at least 1 IM dose entered the long-term follow-up period. ^bSubjects can elect to enter Q4W and Q8W LA extension phase beyond Week 96.

Eron et al. IAS 2017; Paris, France. Slides MOAX0205LB.

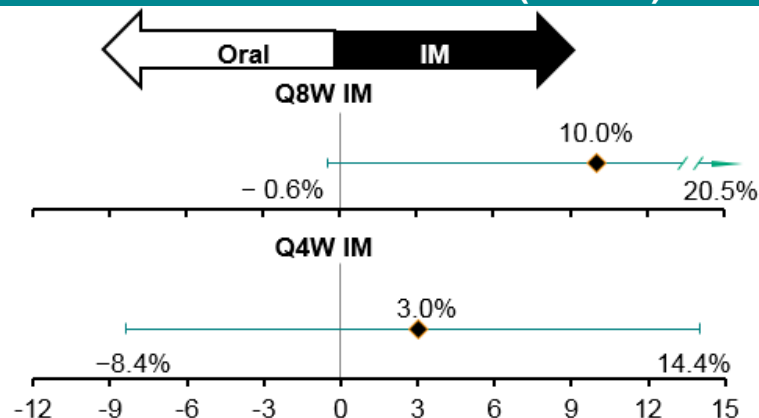
Comparable Response Across Arms

Week 96 HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)

Virologic outcomes



Treatment differences (95% CI)



Week 96 outcomes, n (%)

Virologic response

Virologic nonresponse

Data in window not <50 c/mL^a

Discontinued for lack of efficacy

Discontinued for other reason while not <50 c/mL

No virologic data in window

Discontinued due to adverse event or death

Discontinued for other reasons

Missing data during window but on study

	Q8W IM (n=115)	Q4W IM (n=115)	Oral CAB (n=56)
Virologic response	108 (94)	100 (87)	47 (84)
Virologic nonresponse	5 (4)	0	1 (2)
Data in window not <50 c/mL ^a	2 (2)	0	0
Discontinued for lack of efficacy	1 (<1)	0	1 (2)
Discontinued for other reason while not <50 c/mL	2 (2) ^b	0	0
No virologic data in window	2 (2)	15 (13)	8 (14)
Discontinued due to adverse event or death	1 (<1)	9 (8)	2 (4)
Discontinued for other reasons	1 (<1)	5 (4)	6 (11)
Missing data during window but on study	0	1 (<1)	0

CAB, cabotegravir; CI, confidence interval; IM, intramuscular; ITT-ME, intent-to-treat maintenance exposed; LA, long acting; NRTI, nucleoside reverse transcriptase inhibitor; PO, orally; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

^aWeek 96 HIV-1 RNA, 87 copies per mL, 118 copies per mL. ^bIncludes one subject who withdrew consent because of injection tolerability.

Eron et al. IAS 2017; Paris, France. Slides MOAX0205LB.

9th IAS Conference on HIV Science; July 23-26, 2017; Paris, France

Conclusioni

- ☐ **La terapia antiretrovirale nel paziente con infezione da HIV detenuto rappresenta una sfida**
- ☐ **In Italia sono già stati ottenuti importanti successi per quanto riguarda l'accesso, la continuità delle cure e il raggiungimento del successo virologico**
- ☐ **La disponibilità di nuove strategie e paradigmi terapeutici che uniscono semplicità e tollerabilità rappresenta un sicuro vantaggio nella gestione globale del paziente detenuto**



Prison Health is Public Health“*

*** DUBLIN DECLARATION ON HIV/AIDS IN PRISONS
IN EUROPE AND CENTRAL ASIA, 2004**