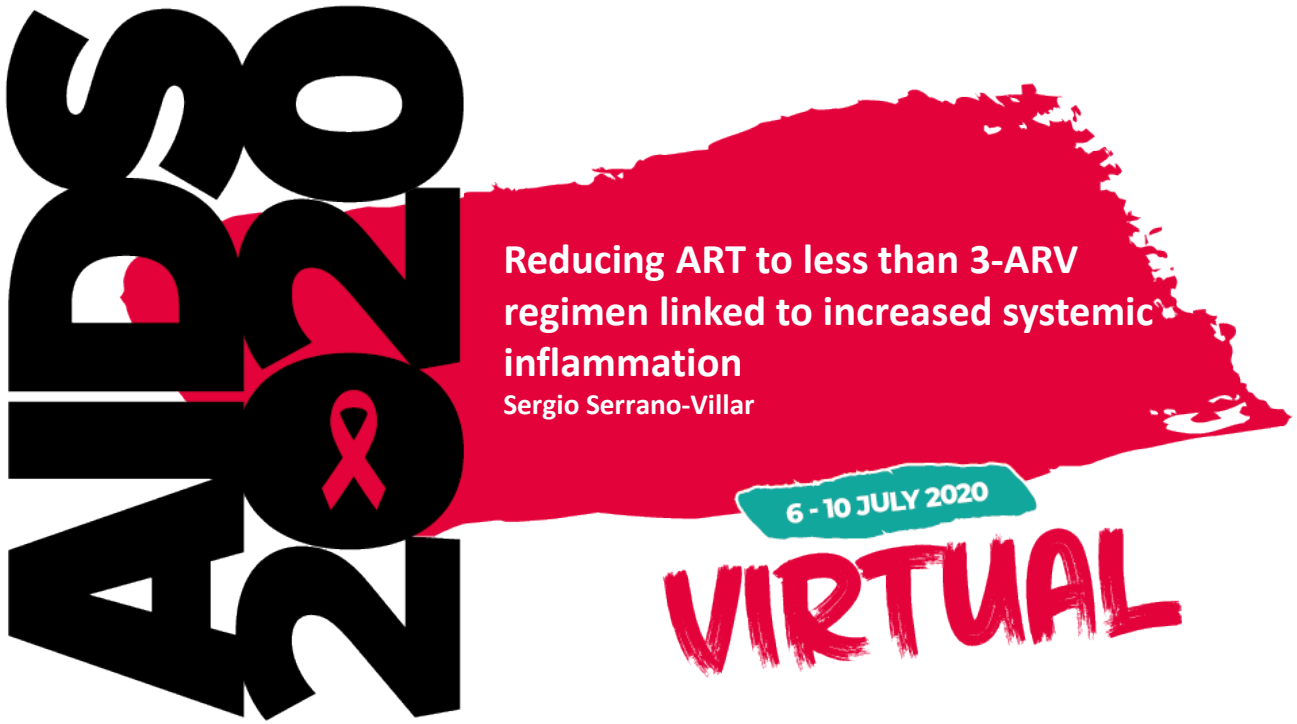


On behalf of all co-authors: María Rosa López-Huertas, Félix Gutiérrez, Manuela Beltrán, Mario Pons, Pompeyo Viciana, Joaquín Portilla, Federico García, Santiago Moreno, and CoRIS (Spanish AIDS Cohort)

Disclosures

- Research funding: MSD, ViiV and Gilead
- Fees for lectures: MSD, Janssen and Gilead
- Consulting: MSD and Gilead

Background

- Cumulative data support the use of several ART combinations with less than 3 ARVs in both treatment-naive and experienced patients.[1,2]
- Increased inflammation persists even during triple ART and strongly predicts adverse clinical outcomes.[3-5]
- Inflammation has been linked with virologic events that occur during ART-mediated suppression:
  - HIV RNA and p24 are likely pro-inflammatory and produced in lymphoid tissues, were many drugs are poorly distributed.[6,7]
  - Suboptimal ART adherence is associated with increased inflammation despite virologic suppression in plasma.[8,9]
- There are no data on the long-term dynamics of inflammatory biomarkers after reduction of the number of antiretrovirals.

1. European AIDS Clinical Society Guidelines. https://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html 2. DHSS Guidelines. https://aidsinfo.nih.gov/guidelines
3. Kuller et al. Plos Medicine 2008. 4. Hunt et al. JID 2014. 5. Tenorio et al. JID 2014
6. Rothenberg et al. PNAS 2015. 7. Imamichi et al. PNAS 2020. 8. Castillo-Mancilla et al. CID 2016. 9. Castillo-Mancilla et al. JIAS 2019.

Impact on clinical outcomes of ART Reduction to <3 Drugs (AIR Study)

Study Design

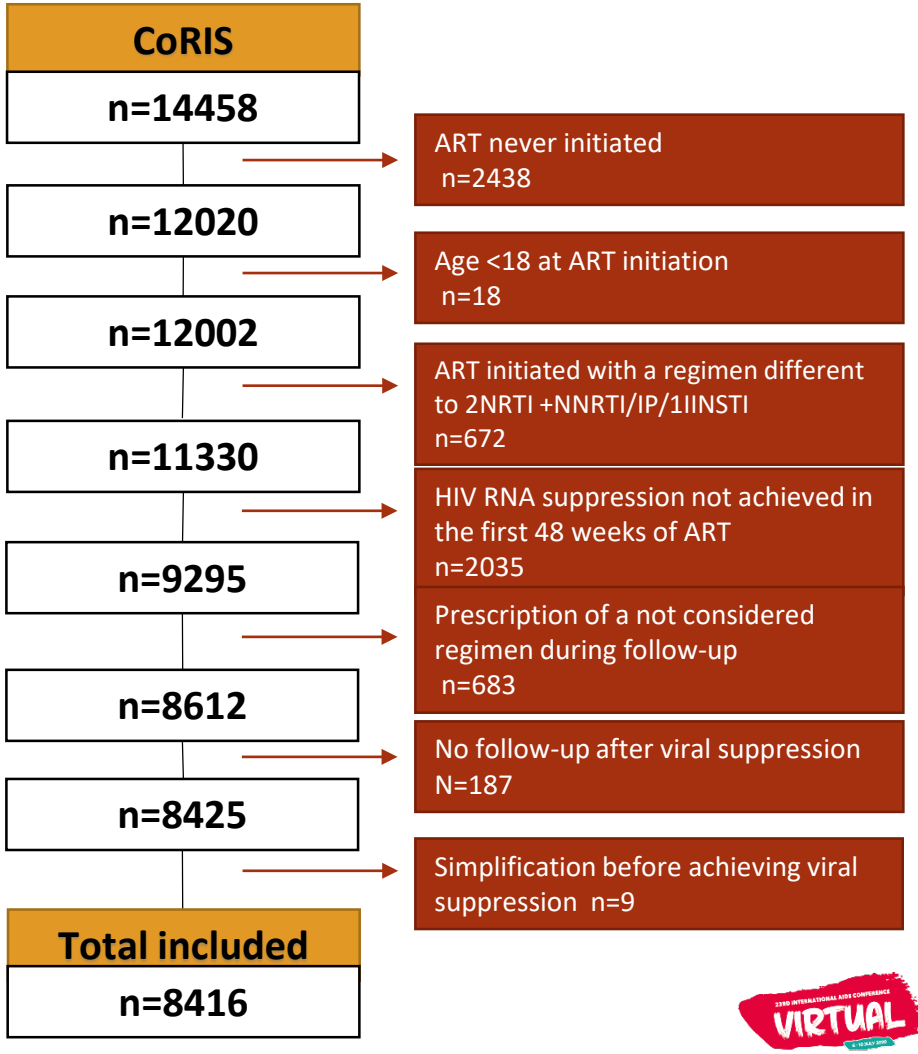
Objective: To assess the effects of switching ART to <3 ARVs on virological failures, clinical events, and systemic inflammation.

Inclusion criteria

- Patients initiating ART in CORIS (Spanish AIDS Cohort) between 2004-2018 with 3DR (2NRTI+bPI/INSTI/NNRTI).
- Virological suppression achieved in the first 48 weeks of ART.
- Either remained on 3DR or switched to 2DR (3TC+bPI, 3TC+DTG, RPV+DTG) or 1DR (LPVr or bDRV).

Exclusion criteria

- ART initiation with regimens with <3 drugs
- Virological failure: ≥2 consecutive viral loads more than 50 copies/mL) during the first 48 weeks of ART
- AIDS conditions or serious non-AIDS events (malignancies, cardiovascular disease, end-stage liver disease, end-stage kidney disease), in the first 48 weeks of ART.



Impact on clinical outcomes of ART Reduction to <3 Drugs (AIR Study)

Methods

- We calculated cause-specific cumulative incidence curves and used multivariate Cox proportional hazards models adjusted for potential confounders to estimate hazard ratios for the endpoints:
  1. Virological failure: ≥2 consecutive viral loads more than 50 copies/mL
  2. Severe non-AIDS events (NAE)
  3. AIDS or AIDS-related death
  4. All-cause death
- Type of regimen (3DR, 2DR, 1DR) was analyzed as a time-varying covariate.
- In a **nested study**, we compared the trajectories of interleukin-6 (IL-6), C reactive protein (CRP), D-dimer and intestinal fatty acid (IFABP) during virologic suppression using piecewise multivariate mixed models.

Severe NAE definition: non-AIDS defining malignancies, cardiovascular disease (myocardial infarction, angina, heart disease, transient ischemic attack, reversible ischemic deficit, stroke, peripheral arteriopathy), end-stage renal disease, end-stage liver disease

Impact on clinical outcomes of ART Reduction to <3 Drugs (AIR Study)

Sociodemographical characteristics

	Remained on 3DR	Changed to 2DR	Changed to 1DR	p-value
	7665 (91.1%)	424 (5%)	327 (3.9%)	
Sex [n (%)]				0.009
Male	6480 (84.5)	323 (80.9)	260 (79.5)	
Female	1185 (15.5)	76 (19.1)	67 (20.5)	
Age				
Median [years (IQR)]	37 (30 – 44)	38 (31 – 45)	37 (30 – 45)	0.02
<50	6763 (88.2)	358 (84.4)	278 (85.0)	0.02
≥50	902 (11.8)	66 (15.6)	49 (15.0)	
Transmission group [n (%)]				0.003
Men who have sex with men	4698 (61.3)	236 (59.1)	166 (50.8)	
Injection drug use	466 (6.1)	25 (6.3)	32 (9.8)	
Heterosexual	2235 (29.2)	118 (29.6)	116 (35.5)	
Other/unknown	266 (3.5)	20 (5.0)	13 (4.0)	
Educational level [n (%)]				<0.001
No or compulsory	2217 (28.9)	148 (34.9)	111 (33.9)	
Upper secondary/University	4097 (53.5)	226 (53.3)	182 (55.7)	
Unknown	1351 (17.6)	50 (11.8)	34 (10.4)	
Country of origin [n (%)]				<0.001
Spain	4739 (61.8)	230 (54.2)	168 (51.4)	
No Spain	2889 (37.7)	191 (45.0)	159 (48.6)	
Unknown	37 (0.5)	3 (0.7)	0	

Impact on clinical outcomes of ART Reduction to <3 Drugs (AIR Study)

Clinical characteristics

Variable	Remained on 3DR	Changed to 2DR	Changed to 1DR	p-value
CD4+ cell count				
Median [cells/ml (IQR)]	321 (198 – 463)	290 (159 – 417)	270 (151 – 366)	<0.001
CD8+ cell count				
Median [cells/ml (IQR)]	900 (62 –1287)	822 (538-1153)	798 (578-1209)	0.001
CD4/CD8 ratio				
Median [cells/ml (IQR)]	0.3 (0.2 – 0.5)	0.4 (0.2 – 0.5)	0.3 (0.2 – 0.4)	<0.001
HIV-1 viral load [n (%)]				
<100000	4749 (62.0)	246 (61.6)	200 (61.2)	0.06
≥100000	2580 (33.7)	144 (36.1)	120 (36.7)	
Unknown	336 (4.4)	9 (2.3)	7 (2.1)	
AIDS diagnosis [n (%)]				
No	6792 (88.6)	351 (88.0)	281 (85.9)	0.31
Yes	873 (11.4)	48 (12.0)	46 (14.1)	
Hepatitis C virus antibodies [n (%)]				
No	4315 (56.3)	204 (51.1)	151 (46.2)	0.001
Yes	680 (8.9)	41 (10.3)	44 (13.5)	
Unknown	2670 (34.8)	154 (38.6)	132 (40.4)	
Hepatitis B surface antigen [n (%)]				
No	4071 (53.1)	225 (56.4)	167 (51.1)	0.001
Yes	196 (2.6)	3 (0.7)	1 (0.3)	
Unknown	3398 (44.3)	171 (42.9)	159 (48.6)	
Year of ART initiation [n (%)]				
2004 – 2007	1176 (15.3)	61 (15.3)	97 (29.7)	<0.001
2008 – 2011	2337 (30.5)	166 (41.6)	162 (49.5)	
2012 – 2014	2087 (27.2)	141 (35.3)	57 (17.4)	
2015 – 2017	2065 (26.9)	31 (7.8)	11 (3.4)	
Time from ART initiation to censoring Median [years (IQR)]	3.8 (2.0 – 6.5)	6.0 (3.8 – 8.4)	7.3 (5.3-9.5)	<0.001

Impact on clinical outcomes of ART Reduction to <3 Drugs (AIR Study)

Risk of virologic failure

	Changed to 2DR	Changed to 1DR
	N = 424	**N = 327**
Switch Regimen		
DTG+RPV	143 (33.7)	
3TC+bDRV	104 (24.5)	
3TC+bATV	75 (17.7)	
3TC+DTG	56 (13.2)	
3TC+LPVr	21 (4.9)	
bDRV		241 (73.7)
LPVr		86 (26.3)
Number of previous ART regimens [N (%)]		
1	226 (53.3)	171 (52.3)
2	107 (25.2)	90 (27.5)
3	41 (9.7)	44 (13.5)
≥4	50 (11.8)	22 (6.7)
Time to switch from virological suppression, years [Median (IQR)]	3.4 (1.8 – 2.9)	2.7 (1.3 – 4.2)
Switch regimen before 6 months from achieving virologic suppression [N (%)]		
No	357 (93.4)	306 (93.6)
Yes	28 (6.6)	21 (6.4)
Median follow up time following switch to <3 Drugs, years [Median (IQR)]	1.0 (0.4–2.0)	1.3 (0.5-3.3)

Impact on clinical outcomes of ART Reduction to <3 Drugs (AIR Study)

Risk of virological failure

Adjusted HR (95% CI) for the association of switching to 1DC or 2DC compared to remaining in 3DR with virological failure

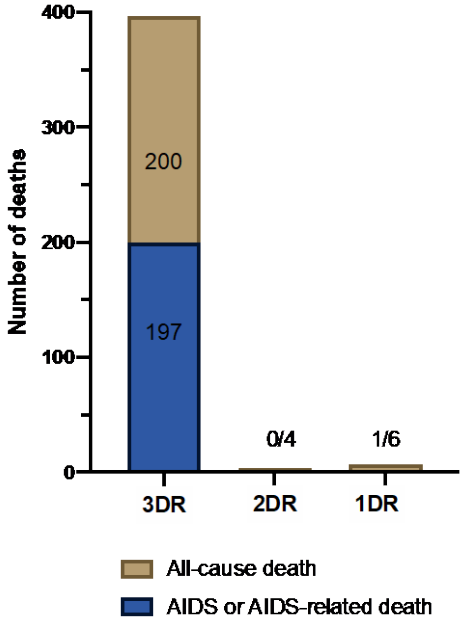
	First 24 months on therapy				
	Events (N)	**HR (95% CI)**	**p-value**	**Adjusted HR (95% CI)**	**p-value**
3DR 2DR 1DR	532 7 36	1.00 0.56 (0.18 – 1.74) 1.15 (0.46 – 2.92)	0.26	1.00 0.91 (0.30 – 2.78) 1.26 (0.50 – 3.19)	0.73
	After 24 months on therapy				
	Events (N)	**HR (95% CI)**	**p-value**	**Adjusted HR (95% CI)**	**p-value**
3DR 2DR 1DR	300 2 13	1.00 1.28 (0.31 – 5.27) 2.83 (1.55 – 5.17)	0.003	1.00 1.55 (0.37 – 6.40) 2.91 (1.56 – 5.43)	0.003

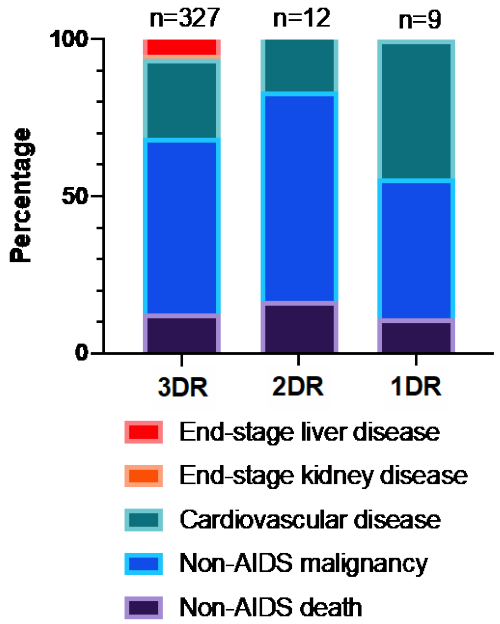
Cox proportional hazards models adjusted for sex, age, transmission group, educational level, country of origin, CD4+ cell count, CD4/CD8 ratio, HIV-1 viral load, AIDS, HCV serostatus, HBsAg positivity, and year of ART initiation.

Greater risk of virological failure with 1DR group but not with 2DR compared to 3DR.

Impact on clinical outcomes of ART Reduction to <3 Drugs (AIR Study)

Risk of any serious NAE or non-AIDS related death



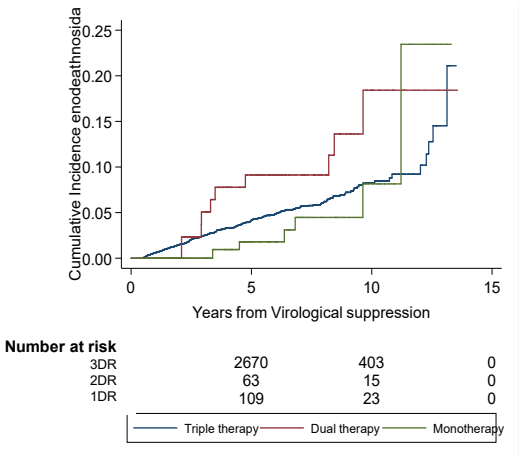


Adjusted HR (95% CI) for the association of with any serious NAE or non-AIDS related death

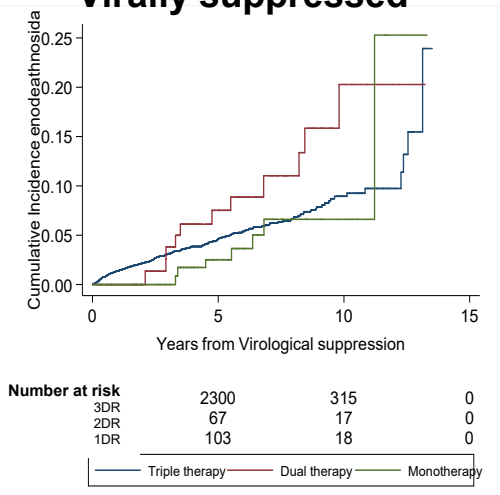
	After 6 months of therapy				
	Events (N)	HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
3DR	266	1.00	0.17	1.00	0.38
2DR	9	1.93 (0.07 – 3.85)		1.65 (0.81 – 3.32)	
1DR	6	1.16 (0.50 – 2.68)		1.10 (0.47 – 2.58)	
	Among those who maintained virological suppression				
	Events (N)	HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
3DR	289	1.00	0.06	1.00	0.25
2DR	11	2.13 (1.13 – 4.01)		1.85 (0.90 – 3.81)	
1DR	7	1.23 (0.56 – 2.67)		1.14 (0.50 – 2.62)	

Cox proportional hazards models adjusted for sex, age, transmission group, educational level, country of origin, CD4+ cell count, CD4/CD8 ratio, HIV-1 viral load, AIDS, HCV serostatus, HBsAg positivity, and year of ART initiation.

After 6 months of therapy



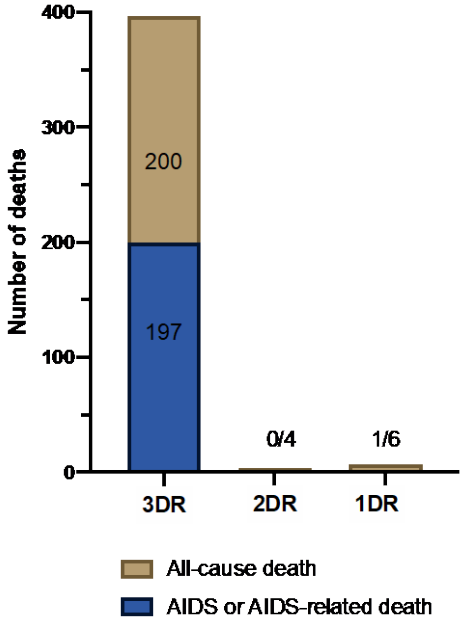
Virally suppressed

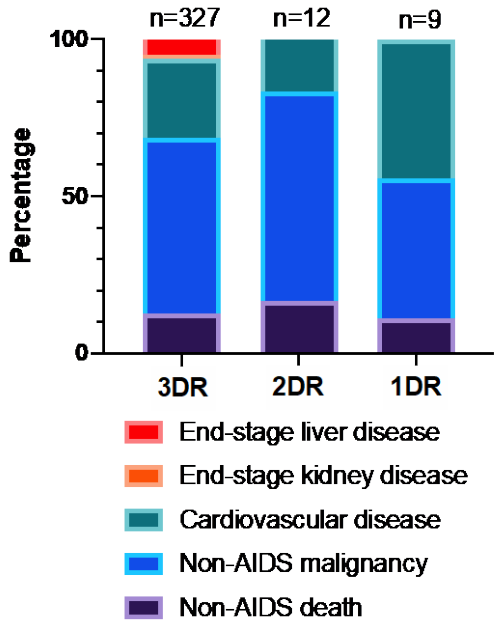


No differences between groups in the risk of serious NAE or non-AIDS related death.
Small absolute number of events in the 2DR and 1DR groups.

Impact on clinical outcomes of ART Reduction to <3 Drugs (AIR Study)

Risk of death from any cause



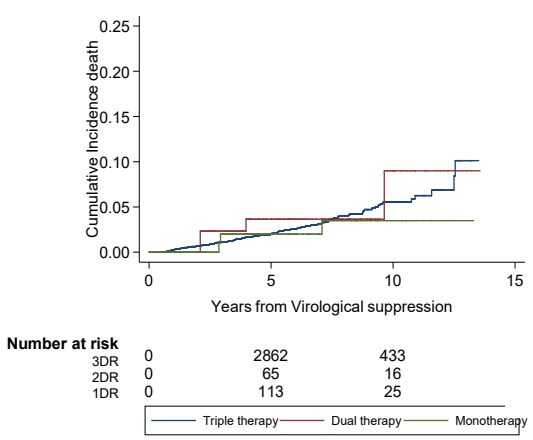


Adjusted HR (95% CI) for the association of with death from any cause

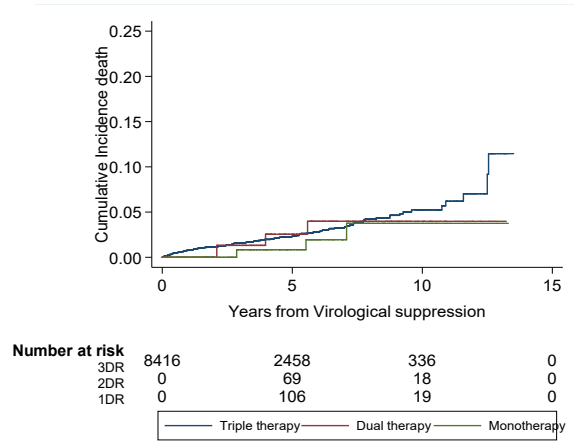
	After 6 months of therapy				
	Events (N)	HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
3DR	157	1.00	0.85	1.00	0.85
2DR	3	1.16 (0.36 – 3.72)		1.23 (0.38 – 4.00)	
1DR	3	0.74 (0.23 – 2.38)		0.77 (0.23 – 2.50)	
	Among those who maintained viral suppression				
	Events (N)	HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
3DR	168	1.00	0.89	1.00	0.96
2DR	3	1.24 (0.38 – 4.02)		1.10 (0.28 – 4.33)	
1DR	3	0.83 (0.25 – 2.69)		0.87 (0.24 – 3.14)	

Cox proportional hazards models adjusted for sex, age, transmission group, educational level, country of origin, CD4+ cell count, CD4/CD8 ratio, HIV-1 viral load, AIDS, HCV serostatus, HBsAg positivity, and year of ART initiation.

After 6 months of therapy



Virally suppressed



No differences between groups in the risk of death from any cause.
Small number of events in the 2DR and 1DR groups.

Impact on Inflammation of ART Reduction to <3 Drugs (AIR Study)

Nested study

90 patients on 3DC
60 patients on 2DC
30 patients on 1DC

Selected based on
At least 3 samples
Longer follow-up

90 patients on 3DR
60 patients on 2DR
30 patients on 1DR

IFABP, IL-6, CRP,
D-dimer

https://www.redris.es/en/web/guest/services/coris

AIR Study. CoRIS 2020

Impact on Inflammation of ART Reduction to <3 Drugs (AIR Study)

ART regimens included

3DR	N=90
ABC+3TC+bDRV	7 (7.8%)
TDF+FTC+bDRV	30 (33.3%)
ABC+3TC+LPVr	1 (1.1%)
FTC+TDF+ATVr	2 (2.2%)
FTC+TAF+DRVc	2 (2.2%)
ABC+3TC+DTG	24 (26.7%)
ABC+3TC+RAL	7 (7.8%)
FTC+TAF+EVGc	4 (4.4%)
FTC+TDF+EVGc	4 (4.4%)
FTC+TDF+DTG	2 (2.2%)
FTC+TDF+RAL	7 (7.8%)

<3DR	Regimen	
2DR N=58	3TC+bATV	2 (34.5%)
	3TC+bDRV	13 (22.4%)
	DTG+3TC	7 (12.1%)
	DTG+RPV	35 (44%)
1DR N=23	LPVr	3 (13%)
	bDRV	20 (87%)

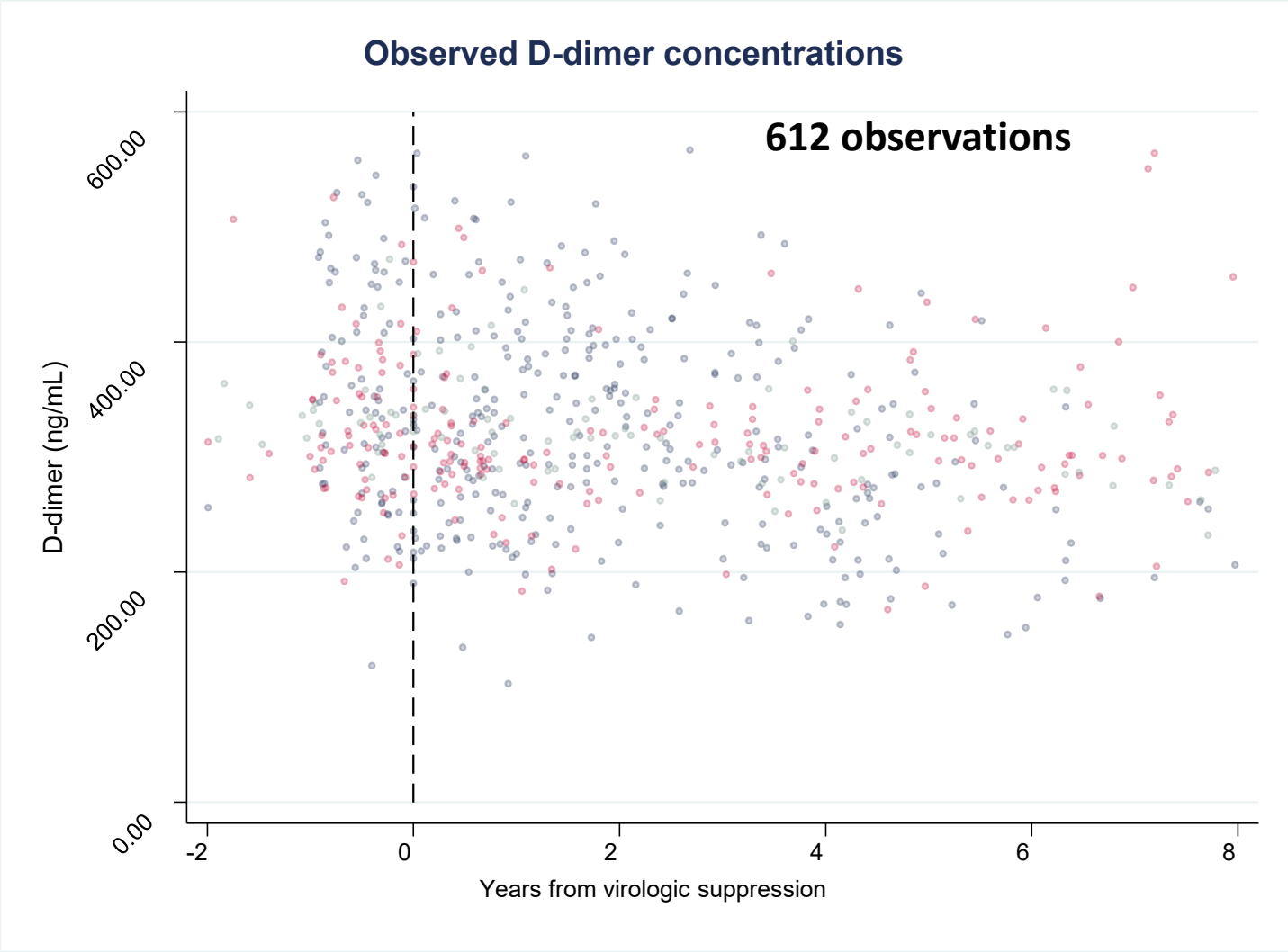
Impact on Inflammation of ART Reduction to <3 Drugs (AIR Study)

Study Population

	All N=148	3DR N=90	2DR N=58	1DR N=23	p value (3DR vs 2DR)	p value (3DR vs 1DR)
Age (mean, [SD])	38 (8)	37 (9)	40 (11)	36 (10)	0.227	0.603
Male, n (%)	149 (86)	78 (87)	50 (86)	18 (78)	0.936	0.314
IDU, n (%)	9 (5)	6 (7)	3 (6)	0 (0)	0.972	0.644
Spanish origin, n (%)	112 (64)	59 (66)	36 (62)	15 (65)	0.666	0.976
Universitary education, n (%)	47 (27)	22 (24)	18 (31)	7 (30.4)	0.593	0.970
AIDS diagnosis, n (%)	23 (13)	15 (16)	8 (14)	1 (4)	0.769	0.157
HCV positive ever, n (%)	19 (11)	12 (13)	6 (10)	1 (5)	0.570	0.290
Maximum HIV-1 RNA (c/mL), median (IQR)	96299 (35632-260000)	114500 (33770-344426)	93599 (36307-219000)	70700 (30910-118000)	0.376	0.077
Time from ART initiation to virologic suppression (years), median (IQR)	0.5 (0.3-0.9)	0.5 (0.2-0.9)	0.5 (0.3-0.9)	0.7 (0.3-0.8)	0.524	0.600
Time from virologic suppression (years) to ART switch, median (IQR)	3 (1.6-4.9)	-	3.5 (1.9-5.2)	1.6 (1.2-1.9)	-	-
Nadir CD4 cell count (cells/µL), median (IQR)	291 (151-394)	300 (151-373)	259 (112-382)	339 (263-448)	0.309	0.061
Number of samples analyzed, median (min, max)	4 (3-11)	4 (3-11)	3 (3-8)	4 (3-7)	<0.001	0.318
Follow-up (years), median (IQR)	4.3 (3-6.2)	3.9 (2.5-4.7)	5.3 (3.9-6.8)	5.8 (3.5-6.8)	<0.001	0.003

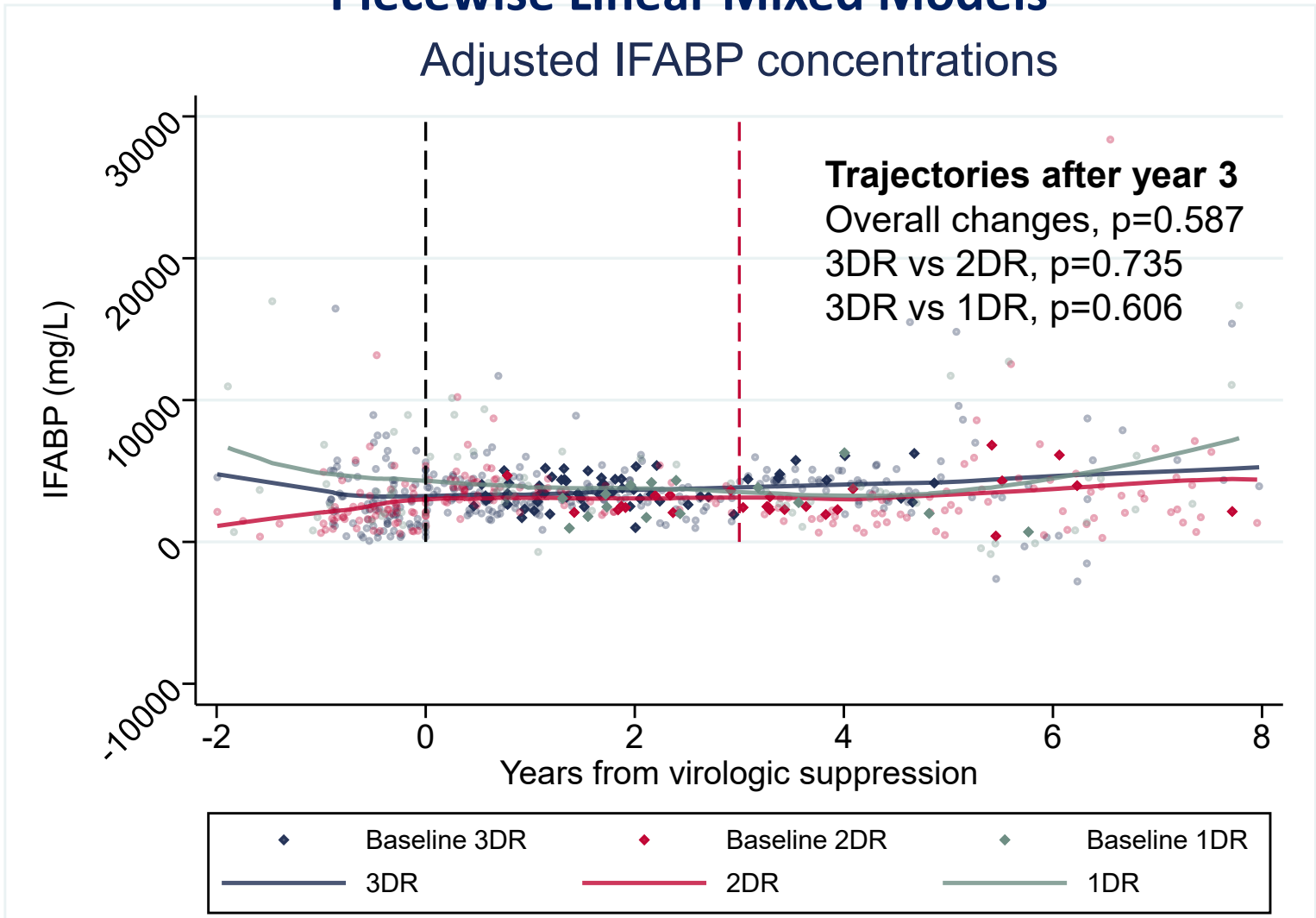
Impact on Inflammation of ART Reduction to <3 Drugs (AIR Study)

Piecewise Linear Mixed Models



Impact on Inflammation of ART Reduction to <3 Drugs (AIR Study)

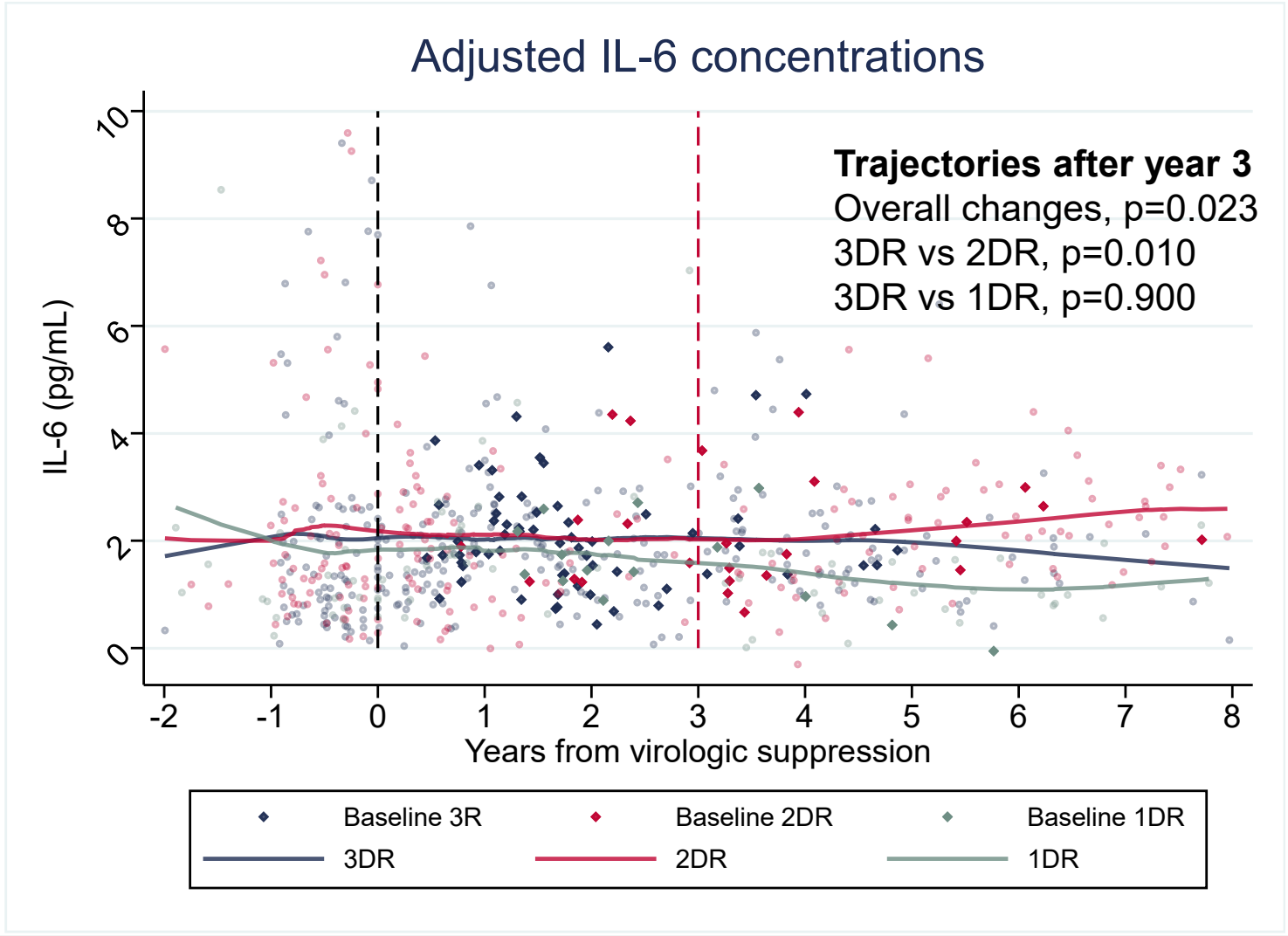
Piecewise Linear Mixed Models



Baseline: for 3DR represents the the second sample after the HIV RNA suppression time point; for 2DR represents the first sample after switch to 2DR.
Linear trajectories estimated using **piecewise linear mixed models** with fixed effects (interaction term biomarker concentration#time, age, sex, risk group, education level, AIDS, CD4 nadir, maximum HIV RNA, biomarker level at HIV RNA suppression).

Impact on Inflammation of ART Reduction to <3 Drugs (AIR Study)

Piecewise Linear Mixed Models

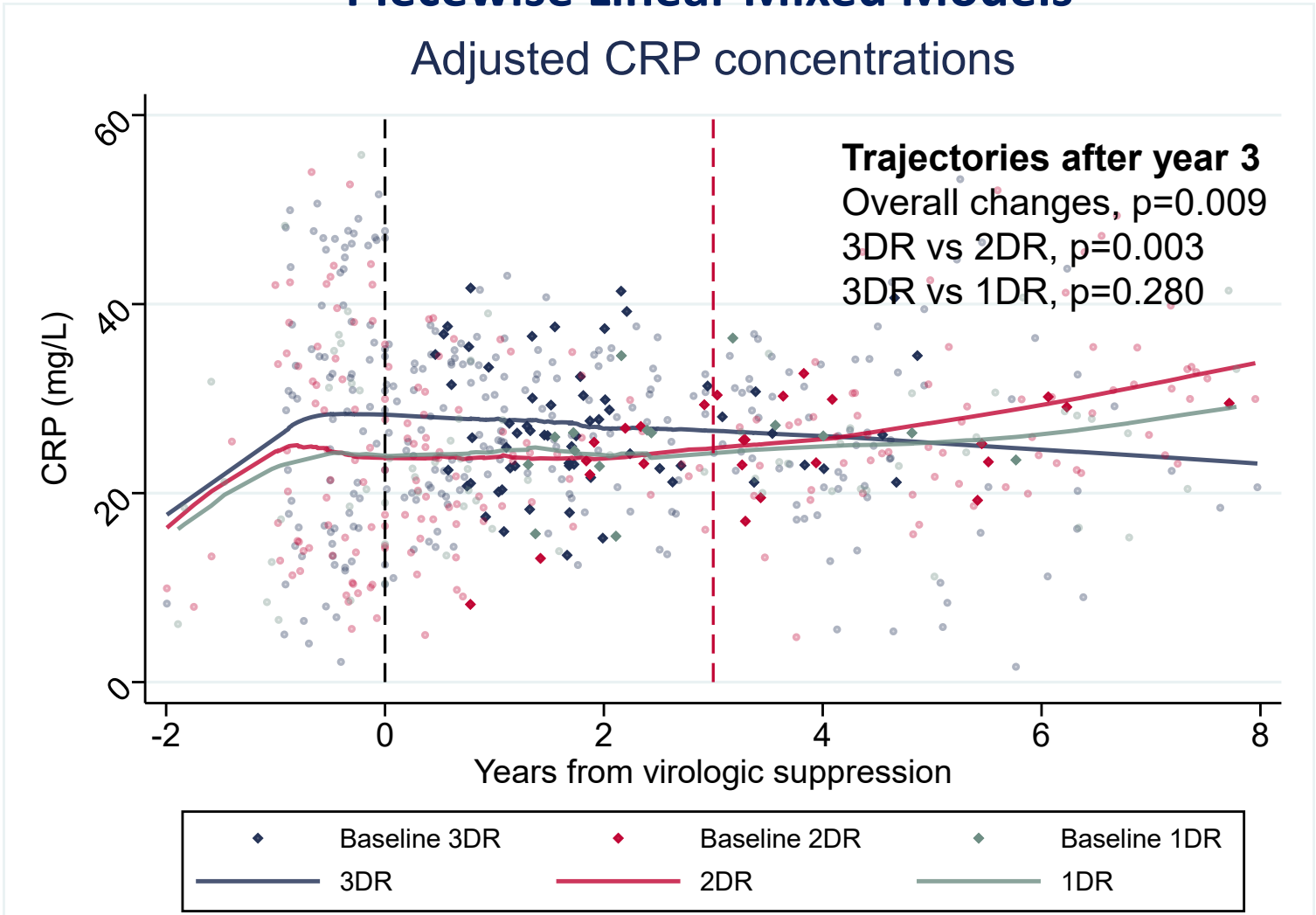


Baseline: for 3DR represents the the second sample after the HIV RNA suppression time point; for 2DR represents the first sample after switch to 2DR.

Linear trajectories estimated using **piecewise linear mixed models** with fixed effects (interaction term biomarker concentration#time, age, sex, risk group, education level, AIDS, CD4 nadir, maximum HIV RNA, biomarker level at HIV RNA suppression).

Impact on Inflammation of ART Reduction to <3 Drugs (AIR Study)

Piecewise Linear Mixed Models

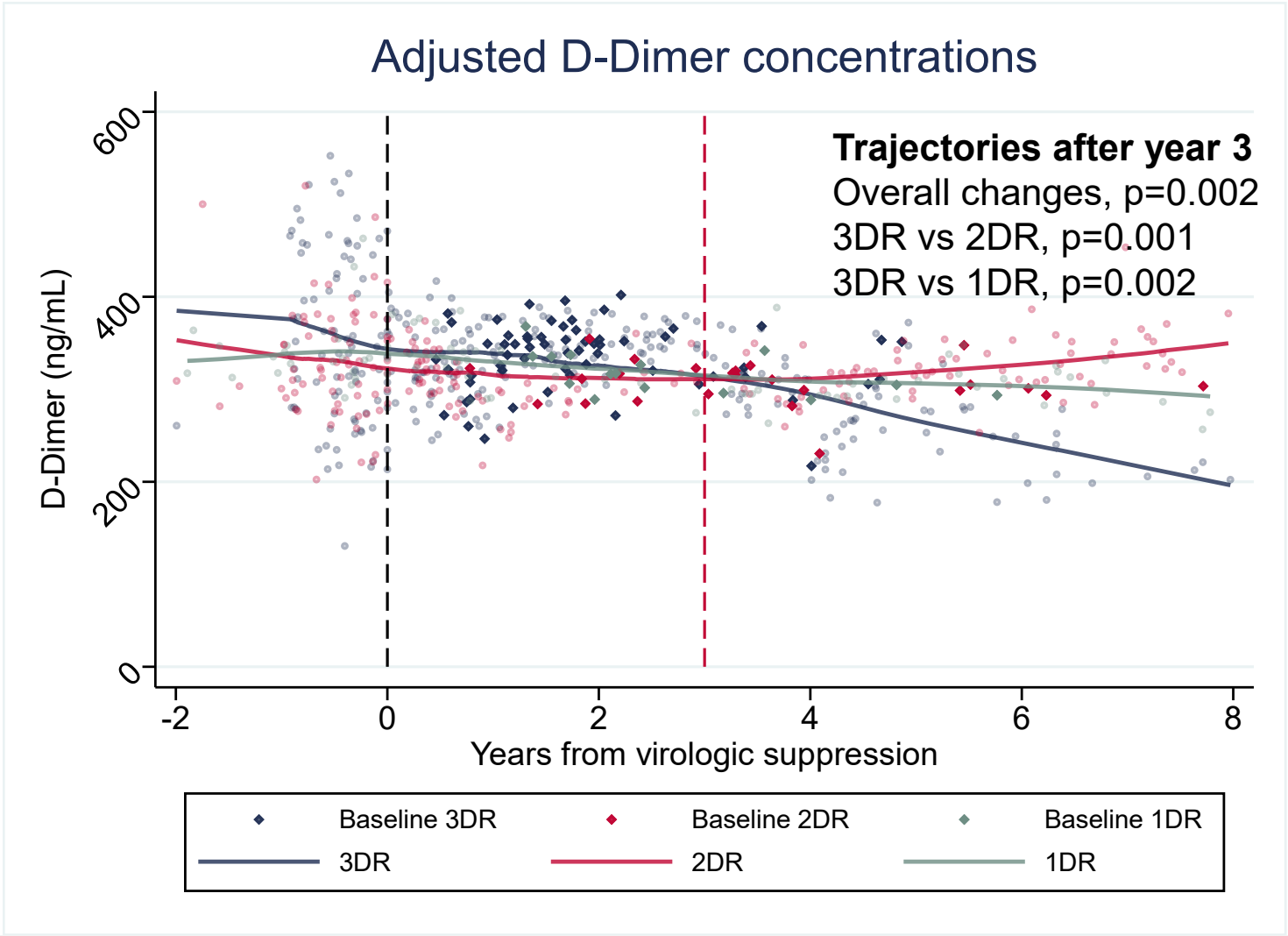


Baseline: for 3DR represents the the second sample after the HIV RNA suppression time point; for 2DR represents the first sample after switch to 2DR.

Linear trajectories estimated using **piecewise linear mixed models** with fixed effects (interaction term biomarker concentration#time, age, sex, risk group, education level, AIDS, CD4 nadir, maximum HIV RNA, biomarker level at HIV RNA suppression).

Impact on Inflammation of ART Reduction to <3 Drugs (AIR Study)

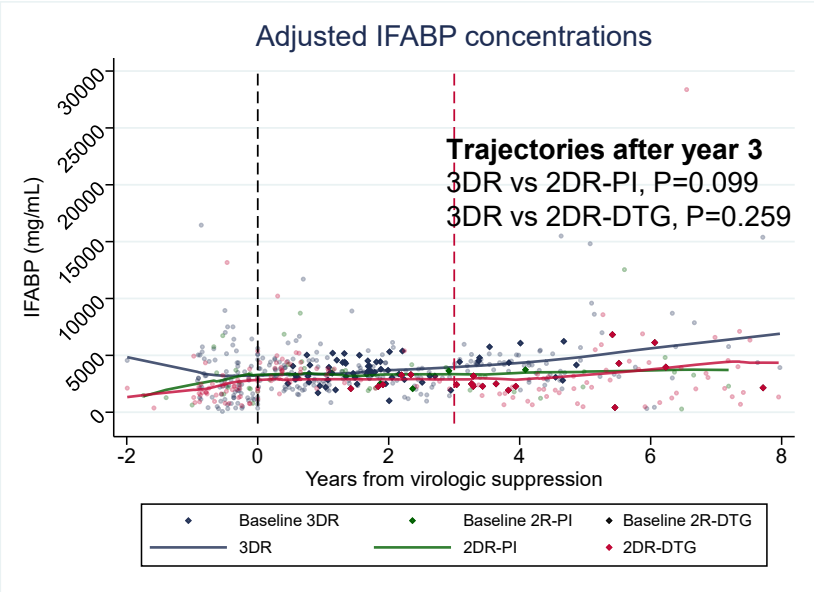
Piecewise Linear Mixed Models

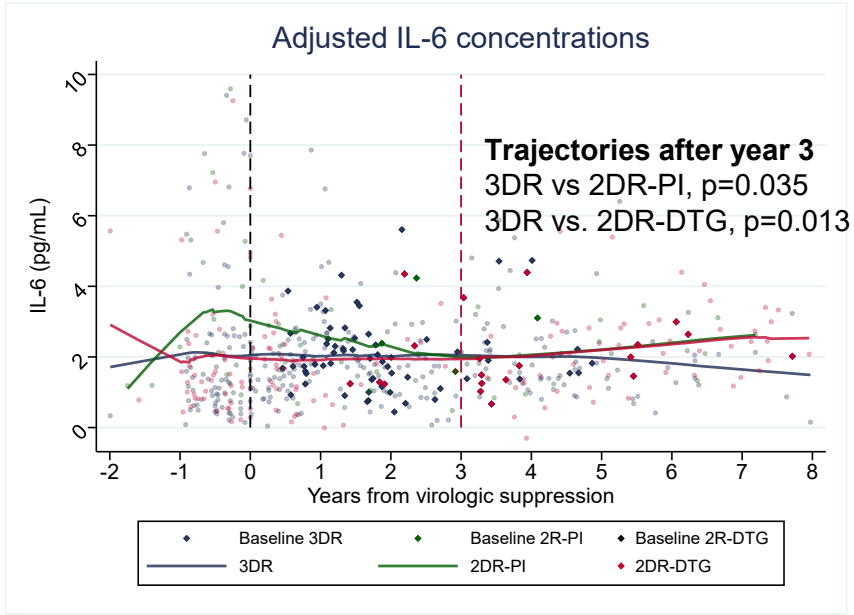


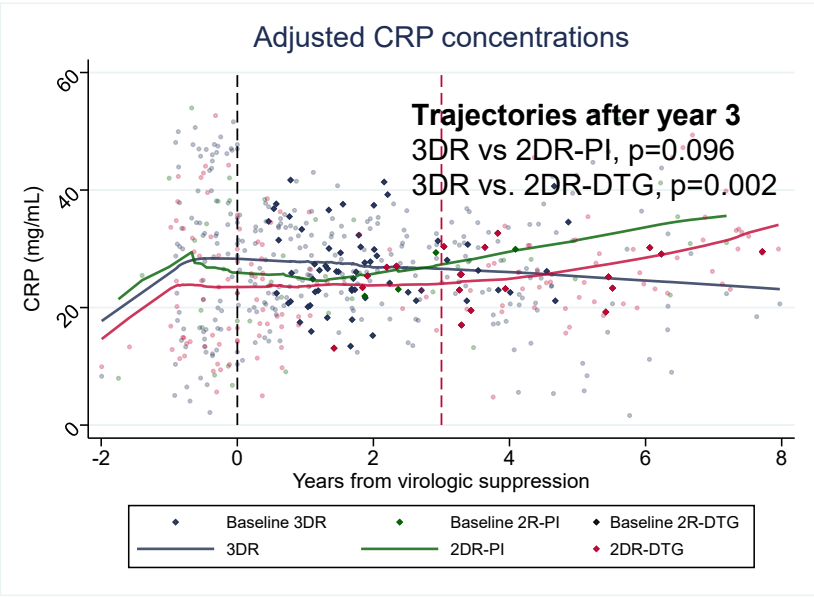
Baseline: for 3DR represents the the second sample after the HIV RNA suppression time point; for 2DR represents the first sample after switch to 2DR.

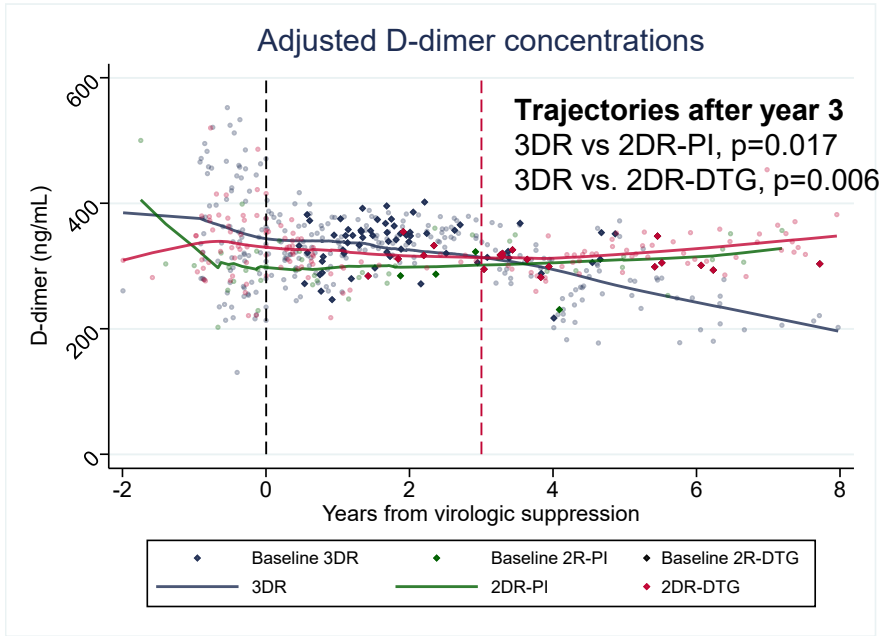
Linear trajectories estimated using **piecewise linear mixed models** with fixed effects (interaction term biomarker concentration#time, age, sex, risk group, education level, AIDS, CD4 nadir, maximum HIV RNA, biomarker level at HIV RNA suppression).

Impact on Inflammation of ART Reduction to <3 Drugs (AIR Study)



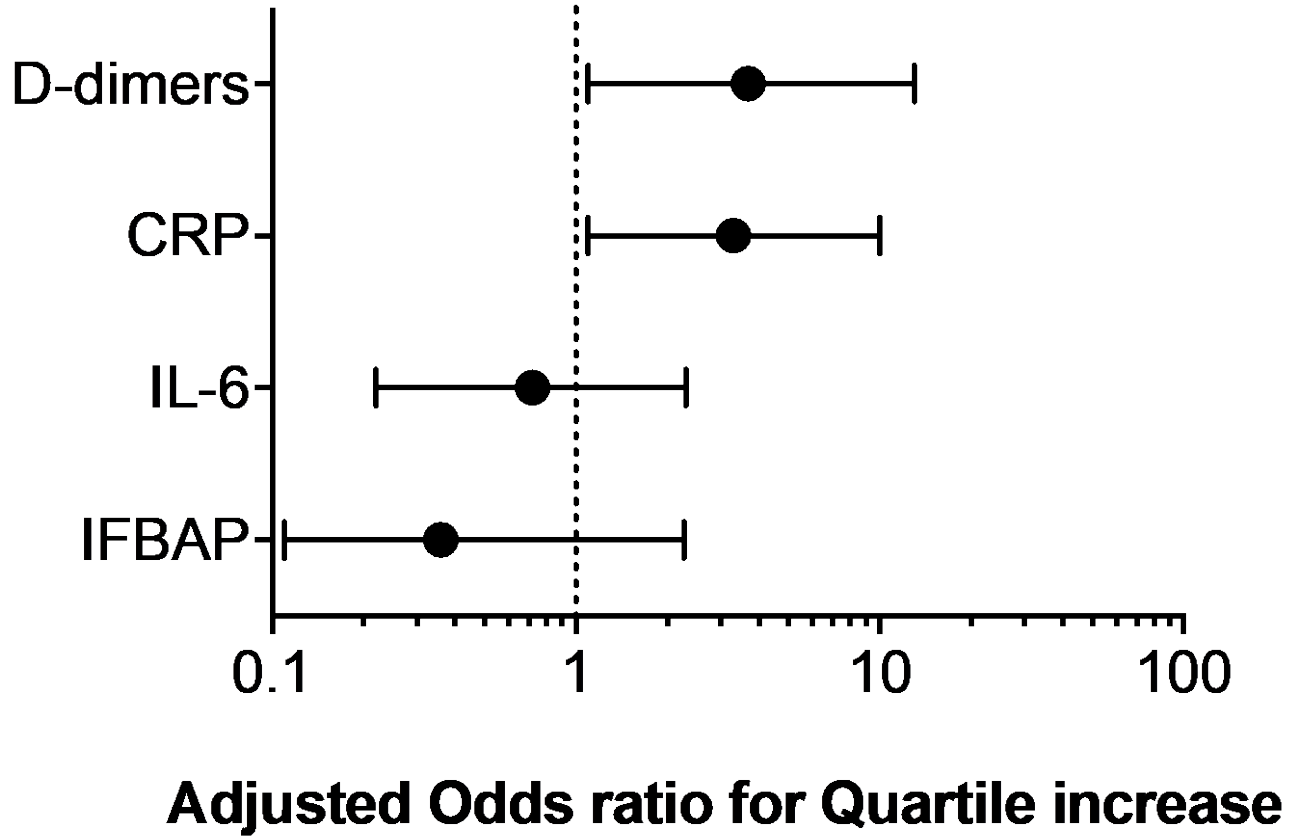






Impact on Inflammation of ART Reduction to <3 Drugs (AIR Study)

Multivariate Logistic regression: changes during follow-up 3DR (ref.) vs. 2DR



Multivariate logistic regression

Adjusted for age, sex, risk group, education level, AIDS, CD4 nadir, maximum HIV RNA, biomarker level at HIV RNA suppression, years of follow-up

Limitations

- **Clinical outcomes analysis:**
  - Low number of AIDS and severe non-AIDS events and mortality limited the statistical power to detect differences in these outcomes.
  - Short median follow-up in the 2DR and 1DR groups after switch (2DR, 1 year and 1DR, 1.2 years).
- **Nested inflammatory study:**
  - Unmeasured confounding (ART adherence) could have affected the inflammatory markers measured.
  - Small number of patients in the 1DR group (N=23).

Conclusions

1. In this large cohort of virologically suppressed individuals, 1DR was associated with a greater risk of virological failure, with no significant differences between 2DR and 3DR.
2. Maintaining 3DR was associated with a more favourable long-term anti-inflammatory profile than switching to 2DR or 1DR.
3. The potential clinical implications of these findings on the development of non-AIDS events deserve further investigation.
4. More information on the effects of different ART strategies on long-term changes of inflammatory biomarkers is needed.

Acknowledgments

Instituto de Salud Carlos III

Centro Nacional de Microbiología

Mª Rosa López-Huertas

Centro Nacional de Epidemiología

Inma Jarrín

Biobank of the Spanish AIDS Cohort

Mª Ángeles Muñoz

CoRIS
Cohorte de la Red de Investigación en Sida

Santiago Moreno

Mario Pons

ENFERMEDADES INFECCIOSAS
H.U RAMÓN Y CAJAL

Funding

This study was funded by Gilead. The funder had no role in the study design, data analysis or the interpretation of the results.

To all patients and their families, who make scientific progress posible.