Effects of ART simplification in the Cohort of the Spanish AIDS Research Network (CoRIS)

Sergio Serrano-Villar[1], Inma Jarrín[2], Pompeyo Viciana[3], Federico Pulido[4], Francesc Vidal[5], Enrique Bernal[6], Carlos E. Galera[7], Santiago Moreno[1], on behalf of the CoRIS

1, Hospital Ramón y Cajal, Madrid. 2, Instituto de Salud Carlos III, Madrid. 3, Hospital Virgen del Rocío, Sevilla. 4, Hospital Doce de Octubre, Madrid. 5, Hospital Joan XXIIII, Tarragona. 6, Hospital Reina Sofía de Murcia, Murcia. 7, Hospital Virgen de la Arrixaca, Murcia

*Corresponding author
Ctra. de Colmenar Km 9,100, 28034 Madrid
Email: sergio.serrano@salud.madrid.org

ABSTRACT #494

INTRODUCTION

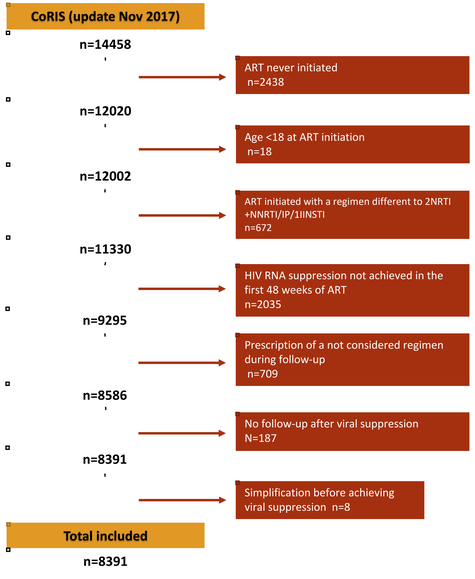
- The number of drugs needed to maintain lifelong HIV RNA suppression is currently debated.
- We aimed to compare the effects of ART simplification strategies on the risk of virological failure in the cohort of the Spanish AIDS Research Network (CoRIS).

METHODS

- We selected ART-naive patients initiating triple ART from 2004 to 2017 in CoRIS who achieved undetectable viral load in the first 48 weeks of ART and either remained in triple therapy during their entire follow-up or were subsequently simplified to dual or monotherapy.
- Patients had to be in one of the three following situations: (i) have remained in triple therapy consisting of 2 NRTI plus either 1 NNRTI or 1 boosted PI or 1 INI during their entire follow-up, (ii) have simplified to dual therapy (3TC + boosted DRV, ATV or LPV, DTG + RPV or DTG + 3TC) or (iii) have simplified to monotherapy (boosted DRV or LPV) sometime after achieving viral suppression.
- The outcome was virological failure, defined as at least two consecutive viral loads >50 copies/ml.
- The type of regimen (triple, dual or mono) and time on regimen were analyzed as time-varying covariates.
- We calculated cause-specific cumulative incidence curves and used multivariate Cox proportional hazards models adjusted for potential confounders to estimate hazard ratios (HR).
- The proportional hazards assumption was checked graphically and by tests based on Schoenfeld residuals.
- HR were calculated for <24 and ≥24 months of ART to meet the proportional hazards assumptions.

RESULTS

Study population – Flow chart



From 14458 patients, 8391 met the inclusion criteria; 7665 remained in triple therapy, 399 switched to dual therapy and 327 to monotherapy.

Sociodemographic characteristics at ART initiation

	Remained on Triple therapy (7665; 91.3%)	Simplified to Dual therapy (399; 4.8%)	Simplified to Monotherapy (327; 3.9%)	p-value
Sex [n (%)]				0.01
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)	39 (31 – 46)	37 (30 – 45)	0.005
<50	6763 (88.2)	335 (84.0)	278 (85.0)	0.01
≥50	902 (11.8)	64 (16.0)	49 (15.0)	
Transmission group [n (%)]				0.003
Homo/bisexual	4698 (61.3)	236 (59.1)	166 (50.8)	
Injecting 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)	138 (34.6)	111 (33.9)	
Upper secondary/University	4097 (53.5)	214 (53.6)	182 (55.7)	
Unknown	1351 (17.6)	47 (11.8)	34 (10.4)	
Country of origin [n (%)]				<0.001
Spain	4739 (61.8)	213 (53.4)	168 (51.4)	
No Spain	2889 (37.7)	183 (45.9)	159 (48.6)	
Unknown	37 (0.5)	3 (0.7)	0	

Clinical characteristics at ART initiation

Variable	Remained on Triple therapy	Simplified to Dual therapy	Simplified to Monotherapy	p-value
CD4+ cell count				
Median [cells/ml (IQR)]	321 (198 – 463)	290 (159 – 417)	270 (151 – 366)	<0.001
<200	1853 (24.2)	121 (30.3)	105 (32.1)	<0.001
200-499	3993 (52.1)	218 (54.6)	181 (55.3)	
≥500	1499 (19.6)	53 (13.3)	30 (9.2)	
Unknown	320 (4.2)	7 (1.7)	11 (3.4)	
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
<0.4	2717 (35.4)	139 (34.8)	143 (43.7)	0.01
≥0.4	1991 (26.0)	103 (25.8)	62 (19.0)	
Unknown	2957 (38.6)	157 (39.4)	122 (37.3)	
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)	
2008 – 2011	2337 (30.5)	166 (41.6)	162 (49.5)	<0.001
2012 – 2014	2087 (27.2)	141 (35.3)	57 (17.4)	
2015 – 2017	2065 (26.9)	31 (7.8)	11 (3.4)	

Multivariable Relative Risk Ratios (RRRs) for sociodemographic and clinical factors associated with simplification to dual- or mono- therapy after virological suppression showed that, compared to triple therapy:

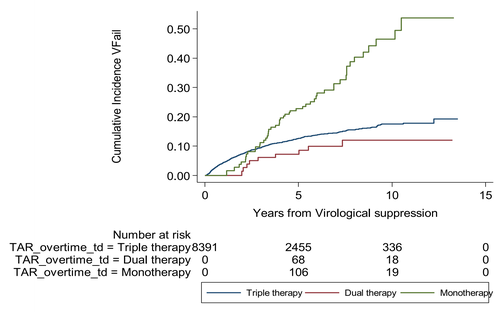
- Participants who simplified during follow-up to dual therapy were older, had higher CD4 counts, higher CD4/CD8 ratio, lower frequency of HBs antigen and earlier year of ART initiation.
- Participants who simplified during follow-up to monotherapy had lower baseline HIV viral load and earlier year of ART initiation.

Characteristics of the simplified ART regimens

	Simplified to Dual therapy N = 399	Simplified to Monotherapy N = 327
Simplified Regimen		
DTG+RPV	143 (35.8)	
3TC+bDRV	104 (26.1)	
3TC+bATV	75 (18.8)	
3TC+DTG	56 (14.0)	
3TC+bLPV	21 (5.3)	
bDRV		241 (73.7)
bLPV		86 (26.3)
Number of previous ART regimens [N (%)]		
1	203 (50.9)	171 (52.3)
2	105 (26.3)	90 (27.5)
3	41 (10.3)	44 (13.5)
≥4	50 (12.5)	22 (6.7)
Time to simplification from virological suppression, years [Median (IQR)]	3.5 (2.0 – 6.1)	2.7 (1.3 – 4.2)
Simplification before 6 months from achieving viral suppression [N (%)]		
No	392 (98.2)	306 (93.6)
Yes	7 (1.8)	21 (6.4)
Maintenance in the simplified therapy		
Yes	333 (83.5)	171 (52.3)
No	66 (16.5)	156 (47.7)
Change to triple therapy	62 (93.9)	111 (71.1)
Change to dual therapy	-	45 (28.9)
Change to monotherapy	4 (6.1)	-
Time from simplification to change of the simplified therapy, years [Median (IQR)]	1.02 (0.46–2.02)	1.32 (0.50-3.28)

The median time of duration of dual therapy and monotherapy was 1 and 1.3 years, respectively.

Cause-specific cumulative incidence curve of virological failure



Adjusted HR (95% CI) for the association of simplification to dual- or mono-therapy compared to remaining in triple with virological failure

First 24 months on therapy

	Nb. events	HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Triple therapy	532	1.00		1.00	
Dual therapy	7	0.56 (0.18 – 1.74)	0.26	0.91 (0.30 – 2.78)	0.73
Monotherapy	36	1.15 (0.46 – 2.92)		1.26 (0.50 – 3.19)	

After 24 months on therapy

	Nb. events	HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Triple therapy	300	1.00		1.00	
Dual therapy	2	1.28 (0.31 – 5.27)	0.003	1.55 (0.37 – 6.40)	0.003
Monotherapy	13	2.83 (1.55 – 5.17)		2.91 (1.56 – 5.43)	

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.

ART regimens
Triple therapy: 2NRTI+1PI; 2NRTI+INSTI; 2NRTI+NNRTI
Dual therapy: DTG+RPV (143), 3TC+bDRV (104), 3TC+bATV (75), 3TC+DTG (56), 3TC+bLPV (21)
Monotherapy: bDRV (241), bLPV (86)

CONCLUSIONS

- **In this large cohort representative of a real-life setting, we found that the durability of the simplified ART regimens was limited and, compared to triple therapy, monotherapy was associated with greater risk of virological failure in the monotherapy group, with no significant differences between dual and triple therapy.**
- **While additional information on long-term outcomes is needed, our results are consistent with the data reported in clinical trials.**

ACKNOWLEDGMENTS
The authors wish to acknowledge all the study participants. This work was supported by the Instituto de Salud Carlos III Redes Temáticas de Investigación en SIDA (ISCIII RETIC RD12/0017/0029 and RD12/0017/0037, RIS-EST37) and was funded by Gilead Sciences.