TENOFOVIR DISOPROXIL FUMARATE AND SEVERITY OF COVID-19 IN PEOPLE WITH HIV INFECTION

Title

00867

Julia Del Amo[1], Rosa Polo[1], Santiago Moreno[2], Esteban Martinez[3], Alfonso Cabello Úbeda[4], José A. Iribarren[5], Adrià Curran[6], Juan Macias[7], Marta Montero[8], Carlos Dueñas[9], Ana Mariño[10], Asun Diaz[11], Jose R. Arribas[12], Inmaculada Jarrín[11], Miguel Hernán[13] and the CoVIHd Collaboration (*)

1 Ministry of Health, MADRID, Spain, 2 University Hospital Ramón y Cajal Madrid, Spain, 3 Hospital Clinic of Barcelona, Barcelona, Spain, 4 Fundacion Jimenez Diaz, Madrid, Spain, 5 Hospital Donostia, San Sebastián, Spain, 6 Hospital Universitario de la Vall d'Hebron,Barcelona, Spain, 7 Hospital Universitario de Valme, Seville, Spain, 8 Hospital Universitario La Fe,Valencia, Spain, 9 University Clinical Hospital of Valladolid, Valladolid, Spain, 10 Ferrol University Hospital, Ferrol, Spain, 11 Institute of Health Carlos III, Madrid, Spain, 12 La Paz University Hospital,Madrid, Spain, 13 Harvard TH Chan School of Public Health, Boston, MA, United States

This article is supported by grant R37AI102634 from the U.S. National Institutes of Health, and the Red Temática de Investigación Cooperativa en Sida (RD06/006, RD 12/0017/0018 and RD 16/0002/0006) and grant COV20/01112. PROYECTOS DE INVESTIGACIÓN SOBRE EL SARS-COV-2 Y LA ENFERMEDAD COVID19 (Institute of Health Carlos III, Spain).

BACKGROUND

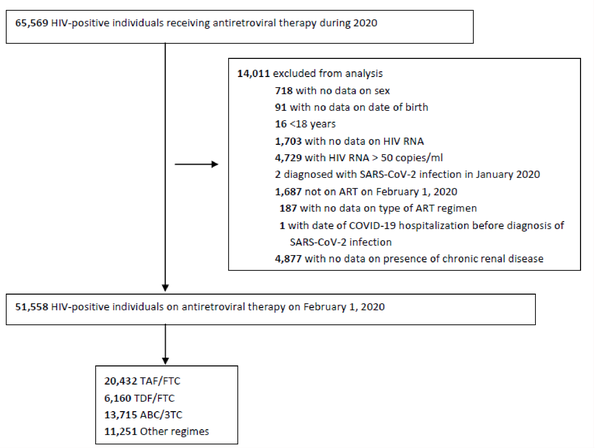
Effective, safe, and affordable antivirals are needed for COVID-19. Several lines of research suggest that tenofovir may be effective against COVID-19 but no large-scale human studies with appropriate adjustment for comorbidities have been conducted.

We describe the incidence, clinical severity and mortality of laboratory-confirmed SARS-CoV-2 infection by antiretroviral therapy(ART) among HIV-positive individuals with virological control adjusting for key potential confounders including hypertension, diabetes, chronic renal disease, cardiovascular disease, and treatment with immunosuppressants or corticosteroids.

METHODS

- We studied HIV-positive individuals on ART in 2020 at 69 HIV clinics in Spain from February 1 to December 31. These 69 clinics serve approximately 44% of all persons on ART with virological suppression in Spain (Figure 1).
- We collected data on socio-demographics, ART, CD4-cell count, HIV-RNA viral load, comorbidities and the following outcomes: laboratory-confirmed SARS-CoV-2 infection,COVID-19 hospitalization, intensive care unit (ICU) admission and death.
- We compared 48-week risks, relative risks, relative differences and 95% confidence intervals (CI) for individuals receiving tenofovir disoproxyl fumarate (TDF)/emtricitabine (FTC), tenofovir alafenamide (TAF)/ FTC, abacavir (ABC)/lamivudine (3TC), and other regimes. All estimates were adjusted for clinical and socio-demographic characteristics via inverse probability weighting.

Figure 1. Flowchart of study population among HIV-positive individuals, CoVIHd Collaboration, Spain, February-December 2020



RESULTS

Of 51,558 eligible individuals, 39.6% were on TAF/FTC, 11.9% on TDF/FTC, 26.6% on ABC/3TC,21.8% on other regimes (Table 1). There were 2,402 documented SARS-CoV-2 infections (425 hospitalizations, 45 ICU admissions, 37 deaths). Compared with TAF/FTC, the estimated risk ratios(RR) (95% CI) of hospitalization were 0.66 (0.43, 0.91) for TDF/FTC and 1.29 (1.02, 1.58) for ABC/3TC, the RRs of ICU admission were 0.28 (0.11, 0.90) for TDF/FTC and 1.39 (0.70, 2.80) for ABC/3TC, and the RRs of death were 0.37 (0.23, 1.90) for TDF/FTC and 2.02 (0.88-6.12) for ABC/3TC. The corresponding RRs of hospitalization for TDF/FTC were 0.49 (0.24, 0.81) in individuals ≥50 years and 1.15 (0.59, 1.93) in younger individuals (Table 2).

Table 1. Baseline characteristics of 51,558 eligible individuals by NRTI combination in HIV-positive individuals, CoVIHd Study, Spain, February-December 2020

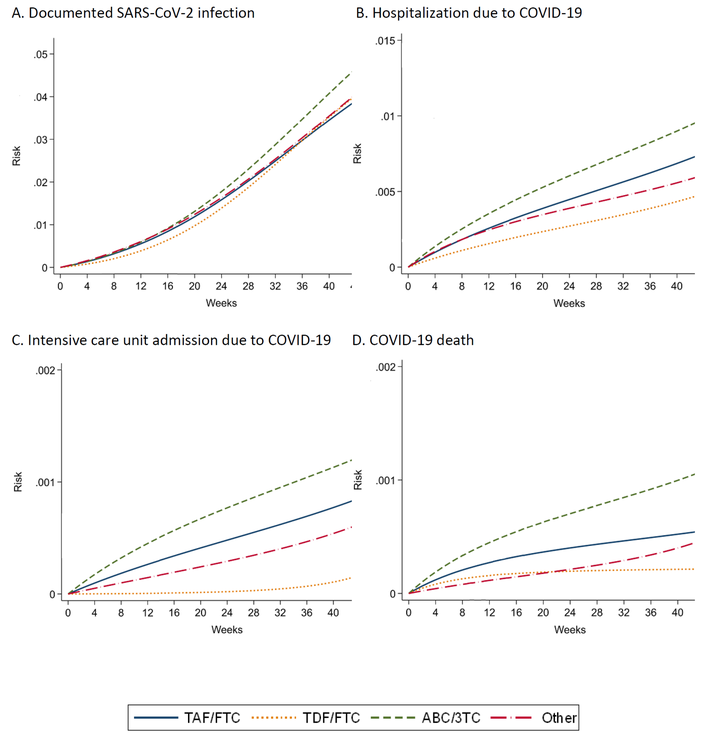
	TAF/FTC N = 20,432 (39.6%)	TDF/FTC N = 6,160 (11.9%)	ABC/3TC N = 13,715 (26.6%)	Other regimes N = 11,251 (21.8%)
Sex [N (%)]				
Men	16,527 (80.9)	4,856 (78.8)	10,797 (78.7)	8,623 (76.6)
Women	3,905 (19.1)	1,304 (21.2)	2,918 (21.3)	2,628 (23.4)
Age, years [Median (IQR)]	49 (39 – 56)	48 (39 – 55)	51 (41 – 57)	53 (45 – 58)
Transmission category [N (%)]				
Heterosexual contact	4,652 (22.8)	1,463 (23.7)	3,218 (23.5)	2,726 (24.2)
Homo/bisexual contact	8,939 (43.7)	2,221 (36.1)	4,859 (35.4)	3,741 (33.2)
Injecting drug use	3,501 (17.1)	1,242 (20.2)	2,665 (19.4)	2,847 (25.3)
Other	503 (2.5)	147 (2.4)	300 (2.2)	328 (2.9)
Unknown	2,837 (13.9)	1,087 (17.6)	2,673 (19.5)	1,609 (14.3)
Country of origin [N (%)]				
Spain	12,632 (61.8)	3,836 (62.3)	8,553 (62.4)	8,077 (71.8)
Other	4,689 (22.9)	1,367 (22.2)	2,325 (16.9)	1,568 (13.9)
Unknown	3,111 (15.2)	957 (15.5)	2,837 (20.7)	1,606 (14.3)
CD4 cell count, cells/mm^3				
Median (IQR)	704 (509-933)	700 (511-929)	746 (536-994)	718 (520-948)
<350	2,059 (10.1)	619 (10.0)	1,179 (8.6)	1,014 (9.0)
350-500	2,775 (13.6)	834 (13.5)	1,735 (12.6)	1,504 (13.4)
>500	15,414 (75.4)	4,671 (75.8)	10,718 (78.1)	8,620 (76.6)
Unknown	184 (0.9)	36 (0.6)	83 (0.6)	113 (1.0)
Hypertension [N (%)]				
No	16,804 (82.2)	5,388 (87.5)	10,897 (79.4)	8,469 (75.3)
Yes	3,091 (15.1)	695 (11.3)	2,589 (18.9)	2,564 (22.8)
Unknown	537 (2.6)	77 (1.2)	229 (1.7)	218 (1.9)
Diabetes [N (%)]				
No	18,490 (90.5)	5,707 (92.6)	12,217 (89.1)	9,736 (86.5)
Yes	1,486 (7.3)	380 (6.2)	1,302 (9.5)	1,305 (11.6)
Unknown	456 (2.2)	73 (1.2)	196 (1.4)	210 (1.9)
Chronic renal disease [N (%)]				
No	19,375 (94.8)	5,952 (96.6)	12,570 (91.6)	10,028 (89.1)
Yes	1,057 (5.2)	208 (3.4)	1,145 (8.3)	1,223 (10.9)
Cardiovascular disease [N (%)]				
No	16,628 (81.4)	5,511 (89.5)	11,759 (85.7)	9,568 (85.0)
Yes	1,051 (5.1)	302 (4.9)	773 (5.6)	887 (7.9)
Unknown	2,753 (13.5)	347 (5.6)	1,183 (8.6)	796 (7.1)
Treatment with immunosuppressants or corticosteroids [N (%)]				
No	13,631 (66.7)	4,313 (70.0)	8,768 (63.9)	7,805 (69.4)
Yes	174 (0.8)	78 (1.3)	163 (1.2)	142 (1.3)
Unknown	6,627 (32.4)	1,769 (28.7)	4,784 (34.9)	3,304 (29.4)

Table 2. Estimated 48-week risks, risk differences and risk ratios of COVID-19 outcomes by NRTI combination in HIV-positive individuals,* CoVIHd Study, Spain, February-December 2020

	Documented SARS-CoV-2 infection				Hospitalization due to COVID-19				ICU admission due to COVID-19				COVID-19 death			
	No. events	Risks (95%CI), %	Risk Differences (95% CI), %	Risk Ratios (95% CI)	No. events	Risks (95%CI), %	Risk Differences (95% CI), %	Risk Ratios (95% CI)	No. events	Risks (95% CI), %	Risk Differences (95% CI), %	Risk Ratios (95% CI)	No. events	Risks (95% CI), %	Risk Differences (95% CI), %	Risk Ratios (95% CI)
TAF/FTC	923	4.3 (4.1, 4.6)	0	1.00	157	0.8 (0.7, 1.0)	0	1.00	17	0.09 (0.05,0.14)	0	1.00	9	0.06 (0.02, 0.11)	0	1.00
TDF/FTC	300	4.5 (3.9, 5.0)	0.16 (-0.48, 0.69)	1.04 (0.89, 1.17)	35	0.5 (0.4, 0.7)	-0.28 (-0.52, -0.08)	0.66 (0.43, 0.91)	2	0.03 (0.01,0.08)	-0.07 (-0.12,-0.004)	0.28 (0.11, 0.90)	1	0.02 (0.02, 0.09)	-0.04 (-0.07, 0.03)	0.37 (0.23, 1.90)
ABC/3TC	687	5.2 (4.8, 5.6)	0.89 (0.40, 1.34)	1.21 (1.09, 1.33)	147	1.1 (0.9, 1.2)	0.24 (0.02, 0.45)	1.29 (1.02, 1.58)	18	0.13 (0.08,0.19)	0.04 (-0.03,0.12)	1.39 (0.70, 2.80)	18	0.12 (0.07, 0.18)	0.06 (-0.01, 0.12)	2.02 (0.88, 6.12)
Other regimes	492	4.6 (4.1, 5.0)	0.24 (-0.27, 0.77)	1.06 (0.94, 1.18)	86	0.7 (0.5, 0.8)	-0.16 (-0.34,0.04)	0.81 (0.62, 1.05)	8	0.07 (0.02,0.12)	-0.02 (-0.09,0.04)	0.76 (0.23, 1.77)	9	0.06 (0.02, 0.11)	0 (-0.06, 0.06)	0.99 (0.34, 2.61)

* Adjusted via inverse probability weighting for age (in years, linear and quadratic terms), sex (male, female), transmission category (heterosexual, homo/bisexual, injecting drug use, other), country of origin (Spain, other), CD4 (<350, 350-500, >500 cells/mm3), and hypertension, diabetes, chronic renal disease, cardiovascular disease, and treatment with immunosuppressants or corticosteroids.

Figure 2. Estimated risks of COVID-19 outcomes by NRTI combination in HIV-positive individuals, *CoVIHd Collaboration, Spain, February-December 2020



* Adjusted via inverse probability weighting for age (in years, linear and quadratic terms), sex (male, female), transmission category (heterosexual, homo/bisexual, injecting drug use, other), country of origin (Spain, other), CD4 (<350, 350-500, >500 cells/mm3), and hypertension, diabetes, chronic renal disease, cardiovascular disease, and treatment with immunosuppressants or corticosteroids.

CONCLUSIONS

- Our findings suggest that, compared with other antiretrovirals, TDF/FTC lowers COVID-19 severity among HIV-positive individuals with virological control. This protective effect may be restricted to individuals aged 50 years and older.
- Confirmatory randomized trials of TDF/FTC for the prophylaxis and early treatment of COVID-19 are warranted.

* CoVIHd Collaboration: Hospital Virgen del Rocío: LF. López Cortés, N. Espinosa, Hospital Universitario Virgen de la Victoria: J. Santos, R.Palacios, Hospital Costa del Sol: J. Olalla, A del Arco Jiménez, Hospital Virgen de las Nieves: C. Hidalgo Tenorio, J.Pasquau, Hospital Universitario Juan Ramón Jiménez: D. Merino,Hospital Regional Universitario de Málaga: M.Castaño, M. Delgado, Hospital Universitario Reina Sofía: A. Rivero, A. Rivero-Juarez, Hospital Universitario Torrecárdenas: A. Collado, Hospital Universitario de Puerto Real: A. Romero, Hospital Clínico Universitario Lozano Blesa: I. Sanjoaquín, Hospital General San Jorge: M. Egido, Hospital Miguel Servet: P. Arazo, R. García, Hospital Insular de Las Palmas: JL. Pérez-Arellano, C. Lavilla, Hospital Universitario de Canarias: JL Gómez Sirvent, MR.Alemán, Hospital Universitario Marqués de Valdecilla: MC. Fariñas, F. Arnaiz de las Revillas, Hospital Universitario de Burgos: C. Navarro-San Francisco Hospital Río Hortega de Valladolid: J. Gómez, Hospital Universitario de León: JM. Guerra, Complejo Asistencial Universitario de Palencia: JJ. Sánchez, Complejo Asistencial Ntra. Sra. de Sonsoles de Ávila: MA. Garcinuño, Hospital General de Segovia: EM.Ferreira, Complejo Hospitalario de Toledo: F. Cuadra, Hospital General La Mancha Centro: JR. Barberá, Hospital Virgen de la Luz: P. Geijo, Hospital General Universitario de Albacete: E. Martínez, Hospital Clínic Barcelona: JL. Blanco, E. de Lazzari Hospital Universitari Vall d'Hebron: V. Falcó, Hospital Universitari de Bellvitge: A. Imaz, D. Podzamczer, Hospital Santa María: E. González, Hospital Universitari Mútua Terrassa: D. Dalmau, Consorci Corporació Sanitària Parc Taulí de Sabadell: G. Navarro, Parc Sanitari Sant Joan de Déu: V. Díaz-Brito, Hospital Universitari Joan XXIII de Tarragona: F. Vidal, Consorcio Sanitario del Maresme (Hospital de Mataró): L. Force, Hospital Dr. Josep Trueta: A. Oller, Consorcio Hospitalario de Vic: I. Vilaró, Consorci Sanitari de Terrasa: M. Aranda, Hospital de Viladecans: A. Lérida, Hospital Sant Jaume de Calella: O. del Río, Hospital de Mollet: P. Vázquez, Fundació Salut Empordà (Figueres): J. Cucurull, Hospital de Palamós: M.Hortos, Hospital de Tortosa Verge de la Cinta: A. Orti, Hospital General de Granollers: E. Deig, Hospital Universitario La Paz- H. Carlos III: R.Montejano, J.Cadiñanos, Hospital Fundación Jiménez Díaz: M.Górgolas, A.Herrero, Hospital Universitario Ramón y Cajal: MJ. Pérez, S. del Campo, Hospital General Universitario Gregorio Marañón: J Berenguer, JC. López, Hospital 12 de Octubre: D. Rial, R. Rubio, Hospital Universitario de La Princesa: I. de los Santos, J. Sanz, Hospital Infanta Leonor-Vallecas: P. Ryan, G.Cuevas, Hospital Universitario Fundación Alcorcón: M. Velasco, Hospital Universitario Príncipe de Asturias: J. Sanz Moreno Hospital Universitario Rey Juan Carlos: S. Nistal, Hospital General de Villalba: J. Hernández, Hospital Universitario Infanta Elena: M. Rubio, Hospital Quirón Salud: D.Carnevali, Hospital Universitario Infanta Sofía: I. Suárez, Hospital Clínico San Carlos: J. Vergas, V. Estrada, Hospital Puerta de Hierro: A. Díaz DE Santiago, S. de la Fuente, Hospital Severo Ochoa-Leganés: M. Cervero, Hospital de Getafe: S. Rodriguez, Complejo Hospitalario de Navarra: M. Rivero, E.Moreno, Hospital Clínico Universitario de Valencia: MJ. Galindo, R. Ferrando, Hospital La Fé: M. Tasias, Hospital General Universitario de Valencia: M García del Toro, Hospital General Universitario de Elche: F. Gutiérrez, Hospital Marina Baixa: C. Amador, Hospital Universitario de la Plana: A. Blasco, Hospital General Universitario de Alicante: X. Portilla, Hospital Arnau de Vilanova-Lliria: J. Flores, C. Tortaiada, Hospital Peset: M. Madrazo, A. Artero, Hospital Álvaro Cunqueiro: G. Pousada, A. Ocampo, Hospital de Santiago de Compostela: A. Antela, E. Losada, Hospital Universitari Son Espases: M. Riera, F. Alberti, Hospital San Pedro – CIBIR: JR. Blanco, Hospital de Donostia: MA. Von Wichmann, Hospital de Basurto: M.de la Peña, I Lombide, Hospital Universitario Araba: JJ. Portu, Hospital Osi Barakaldo-Sestao: R. Silvariño, Hospital Universitario de Cruces: J. Goikoetxea, E.Bereciartua, Hospital Universitario Central de Asturias: V. Asensi, M. Rivas-Carmenado, Hospital Clínico Universitario Virgen de la Arrixaca: C. Galera, Hospital General Universitario Reina Sofía: E. Bernal.