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Comorbidity burden and outcomes with long-acting cabotegravir plus rilpivirine in the RELATIVITY cohort

Jesús Troya[a], Carmen Busca[b], Mariano Matarranz[a], María José Galindo[c], María Fernández-Regueras[d], María Belén Sánchez-López[e], Dácil García-Rosado[f], Miguel Torralba[g], Alberto Díaz De Santiago[h], Francisco Fanjul[i], Adrián Rodríguez[j], Alfonso Cabello-Úbeda[k], María José Crusells-Canales[l], María del Carmen Navarro[m], Ignacio De los Santos[n], Carmen Hidalgo[o], Luis Enrique Morano-Amado[p], David Vinuesa-García[q], Carlos De Andrés David[r], Enrique Bernal[s], Ruth Caballero[t], Alberto Romero[u], Juan Tiraboschi[v], Alejandra Gimeno-García[w], Eva María Ferreira[x], Juan Emilio Losa-García[y] and Luis Buzón-Martín[d]

In RELATIVITY, among 3118 virologically suppressed people with HIV switching to long-acting cabotegravir plus rilpivirine, 40.0% had at least one comorbidity and 16.8% had multimorbidity. Higher comorbidity burden identified older, clinically complex participants with longer ART exposure, lower CD4 nadir, and more prior AIDS. Virological failure (0.6–0.8%), definitive discontinuation (4.3–6.3%), and complete injection coverage, defined as proportion of days covered (PDC) of 100% (83.4–87.2%) were similar across strata, suggesting that comorbidity burden alone should not preclude individualized use in routine care.

Introduction

People with HIV (PWH) are aging, and HIV care increasingly resembles chronic disease management [1–3]. As survival improves, non-AIDS comorbidities accumulate earlier and cluster more frequently in PWH than in comparator populations [4,5]. Cardiovascular and cardiometabolic diseases are major contributors to this burden [6–8]. Long-acting cabotegravir plus rilpivirine (CAB+RPV LA) removes daily oral dosing but shifts adherence to scheduled clinic-based injections. In patients with greater clinical complexity, real-world performance may therefore depend not only on virological eligibility but also on the feasibility of maintaining timely injection visits. We evaluated whether baseline comorbidity burden, among virologically suppressed PWH considered eligible for CAB+RPV LA in routine care, was associated with virological durability, adherence to scheduled injections, or treatment persistence after switching.

Methods

The RELATIVITY study is a nationwide ambispective cohort of PWH receiving CAB+RPV LA in routine care across 58 Spanish hospitals [9]. Adults initiating CAB+RPV LA before December 31, 2024, were eligible with HIV-1 RNA < 50 copies/ml at initiation; those with baseline viremia or undocumented suppression were excluded. The database was locked on March 1, 2025. Of the 3146 virologically suppressed participants, 3118 had sufficient baseline information for comorbidity classification and were included in this analysis.

Comorbidity was defined as any recorded non-AIDS chronic condition. Comorbidity burden was defined as the number of recorded comorbidities; and multimorbidity was defined as two or more recorded comorbidities. Recorded conditions were additionally grouped into nonmutually exclusive predefined phenotypes: cardiometabolic risk, established cardiovascular disease, chronic kidney disease, chronic liver disease of nonmetabolic origin, neuropsychiatric disorders, chronic pulmonary disease, and inactive oncologic disease. Virological failure was defined as two consecutive HIV-1 RNA values ≥ 200 copies/ml or one value ≥ 500 copies/ml leading to treatment discontinuation. Adherence to scheduled injections was assessed using the proportion of days covered (PDC), defined as the proportion of follow-up days with valid injectable treatment within permitted administration windows. Cox models adjusted for age, sex, and comorbidity phenotypes were exploratory because events were uncommon.

Results

Among the 3118 participants, 1870 (60.0%) had no comorbidities, 725 (23.3%) had one comorbidity, and 523 (16.8%) had multimorbidity (Table 1). The increasing comorbidity burden captured a clear gradient of baseline complexity: median age increased from 41.0 to 57.1 years, prior ART exposure from 8.0 to 15.0 years, and time with viral suppression from 72 to 120 months across the no-comorbidity and multimorbidity groups. Participants with multimorbidity also had lower CD4 nadir, higher body mass index, more smoking, alcohol use disorder, and higher proportions with prior AIDS and previous virological failure. The cardiometabolic phenotype was the most prevalent and showed the most frequent co-occurrence, particularly with neuropsychiatric and chronic liver phenotypes (Supplementary Figure, https://links.lww.com/QAD/D962). Reasons for switching were largely

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Table 1. Comorbidity burden, baseline complexity, and outcomes after switching to CAB+RPV LA.

Characteristic/outcome	No comorbidities ($n=1870$)	One comorbidity ($n=725$)	Multimorbidity ≥2 comorbidities ($n=523$)	*P* values
Baseline demographic and behavioral profile				
Age, years, median [IQR]	41.0 [34.0;48.0]	49.0 [41.0;56.0]	57.1 [51.6;63.0]	<0.001
Female sex, *n/N* (%)	224/1,870 (12.0)	125/725 (17.2)	116/523 (22.2)	<0.001
Spanish nationality, *n/N* (%)	1,202/1,862 (64.6)	538/723 (74.4)	432/522 (82.8)	<0.001
Smoking, *n/N* (%)	505/1,870 (27.0)	224/725 (30.9)	192/523 (36.7)	0.001
Alcohol use disorder, *n/N* (%)	158/1,870 (8.4)	76/725 (10.5)	72/523 (13.8)	<0.001
Drug use, *n/N* (%)	544/1,727 (31.5)	232/687 (33.8)	173/495 (34.9)	0.273
BMI, kg/m^2, median [IQR]	24.3 [21.6; 27.0]	25.2 [22.1; 28.3]	25.8 [22.5; 28.9]	<0.001
HIV acquisition and history				
Heterosexual transmission, *n/N* (%)	284/1,870 (15.2)	164/725 (22.6)	136/523 (26.0)	<0.001
Injecting drug use transmission, *n/N* (%)	34/1,870 (1.8)	56/725 (7.7)	106/523 (20.3)	<0.001
GBMSM transmission, *n/N* (%)	1,326/1,870 (70.9)	414/725 (57.1)	211/523 (40.3)	<0.001
Time from diagnosis to ART initiation, months, median [IQR]	1.7 [0.0; 10.0]	2.1 [1.0; 21.8]	4.0 [1.0; 38.0]	<0.001
Years on ART before CAB+RPV LA, median [IQR]	8.0 [4.0; 12.0]	10.0 [6.4; 17.0]	15.0 [10.0; 23.0]	<0.001
Suppression time before CAB+RPV LA, months, median [IQR]	72.0 [25.0; 120.0]	94.0 [48.0; 142.5]	120.0 [68.0; 186.0]	<0.001
Baseline INSTI-based ART, *n/N* (%)	1,476/1,870 (78.9)	543/725 (74.9)	383/523 (73.2)	0.007
Previous virological failure, *n/N* (%)	40/1,870 (2.1)	28/725 (3.9)	38/523 (7.3)	<0.001
Prior AIDS diagnosis, *n/N* (%)	163/1,870 (8.7)	118/725 (16.3)	105/523 (20.1)	<0.001
CD4 nadir, cells/mm3, median [IQR]	369.5 [234.0; 521.5]	306.0 [167.0; 480.0]	260.0 [119.5; 433.0]	<0.001
Reasons for switching to CAB+RPV LA				
Toxicity, *n/N* (%)	21/1,870 (1.1)	9/725 (1.2)	18/523 (3.4)	0.001
Drug interaction, *n/N* (%)	3/1,870 (0.2)	4/725 (0.6)	5/523 (1.0)	0.019
Simplification, *n/N* (%)	436/1,870 (23.3)	176/725 (24.3)	130/523 (24.9)	0.716
Convenience/quality of life, *n/N* (%)	1,000/1,870 (53.5)	369/725 (50.9)	225/523 (43.0)	<0.001
Swallowing disorder, *n/N* (%)	4/1,870 (0.2)	7/725 (1.0)	5/523 (1.0)	0.011
Patient request, *n/N* (%)	654/1,870 (35.0)	274/725 (37.8)	214/523 (40.9)	0.033
Follow-up, immunological status and outcomes				
Follow-up time, months, median [IQR]	14.5 [9.0; 19.1]	14.6 [9.0; 19.1]	14.1 [9.0; 19.3]	0.379
Baseline CD4+ T-cell count, cells/ mm^3, median [IQR]	776 [580; 1,035]	770 [578; 1,004]	786 [585; 1,058]	0.476
Baseline CD8$^+$ T-cell count, cells/mm^3, median [IQR]	819 [580; 1,088]	795 [569; 1,074]	850 [599; 1,116]	0.039
Baseline CD4/CD8 ratio, median [IQR]	1.0 [0.7; 1.3]	1.0 [0.7; 1.3]	1.0 [0.6; 1.3]	0.325
Last-visit CD4$^+$ T-cell count, cells/mm^3, median [IQR]	780 [599; 977]	760 [558; 975]	772 [579; 979]	0.098
Last-visit CD8+ T-cell count, cells/mm^3, median [IQR]	761 [576; 994]	746 [536; 989]	772 [559; 1,057]	0.174
Last-visit CD4/CD8 ratio, median [IQR]	1.0 [0.8; 1.4]	1.0 [0.7; 1.4]	1.0 [0.7; 1.4]	0.486
Protocol-defined virological failure, *n/N* (%)	11/1,870 (0.6)	6/725 (0.8)	3/523 (0.6)	0.774
Temporary interruption/oral bridging, *n/N* (%)	18/1,870 (1.0)	8/725 (1.1)	5/523 (1.0)	0.966
Definitive discontinuation, *n/N* (%)	97/1,870 (5.2)	31/725 (4.3)	33/523 (6.3)	0.288
- Discontinuation due to injection-site reaction, *n/N* (%)	25/1,870 (1.3)	11/725 (1.5)	8/523 (1.5)	0.854
- Discontinuation due to systemic adverse event, *n/N* (%)	15/1,870 (0.8)	3/725 (0.4)	9/523 (1.7)	0.047
- Discontinuation due to other recorded reasons, *n/N* (%)	75/1,870 (4.0)	14/725 (1.9)	23/523 (4.4)	0.015
Adherence to scheduled injections according to PDC				
PDC 100%, *n/N* (%)	1,501/1,800 (83.4)	599/709 (84.5)	437/501 (87.2)	0.104
PDC 90–99.9%, *n/N* (%)	265/1,800 (14.7)	99/709 (14.0)	60/501 (12.0)	0.297
PDC <90%, *n/N* (%)	34/1,800 (1.9)	11/709 (1.6)	4/501 (0.8)	0.231

ART, antiretroviral therapy; BMI, body mass index; CAB+RPV LA, long-acting cabotegravir plus rilpivirine; GBMSM, gay, bisexual, and other men who have sex with men; INSTI, integrase strand-transfer inhibitor; PDC, proportion of days covered. Values are *n/N* (%) unless otherwise stated. Multimorbidity was defined as two or more recorded comorbidities. Comorbidity phenotypes were nonmutually exclusive. *P* values were descriptive and were not adjusted for multiplicity.
Discontinuation reasons were not mutually exclusive; more than one reason could be recorded for the same participant.

patient-centered, although toxicity, drug interaction, and swallowing-related reasons were more frequently recorded among participants with comorbidity.

Despite this profile, virological outcomes were preserved. Protocol-defined virological failure occurred in 20/3,118 participants (0.6%) and was not more frequent with increasing burden: 11/1,870 (0.6%) without comorbidities, 6/725 (0.8%) with one comorbidity, and 3/523 (0.6%) with multimorbidity. HIV-1 RNA detectability at scheduled visits was infrequent, and observed suppression remained ≥96% through month 21 among participants with available viral-load data. Persistence was high, with 2,957/3,118 participants (94.8%) remaining on CAB +RPV LA without definitive discontinuation.

Adherence to scheduled injections was also maintained. Among participants with evaluable injection-schedule data, a PDC of 100% was observed in 83.4%, 84.5%, and 87.2% across the three burden strata, whereas PDC < 90% was uncommon (1.9%, 1.6%, and 0.8%). Temporary interruption or oral bridging occurred in approximately 1%

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of the participants in each group. Definitive discontinuation was infrequent and similar across the strata (5.2%, 4.3%, and 6.3%). Discontinuation due to injection-site reactions was rare (1.3–1.5%). Systemic adverse-event discontinuation was also uncommon, although it was recorded slightly more often with multimorbidity (1.7%) than without comorbidities (0.8%).

Exploratory Cox models adjusted for age, sex, and comorbidity phenotypes showed no consistent association with virological failure or definitive discontinuation. Some point estimates were above unity for less prevalent phenotypes, but confidence intervals were wide and crossed 1.0, reflecting the low number of events and limited precision. These findings indicate no consistent risk signal, but do not establish absence of risk in every subgroup.

Discussion

Multimorbidity does not necessarily imply poorer adherence, but it commonly coexists with polypharmacy, drug-drug interactions, neuropsychiatric disease, competing appointments, and barriers to treatment continuity, all of which may influence adherence and persistence in both oral and long-acting ART models [10–14]. These factors could plausibly affect a clinic-based injectable strategy that requires scheduled attendance. The present findings extend the efficacy evidence from selected CAB+RPV LA trials [15–18] and are consistent with implementation-focused literature emphasizing that long-acting ART changes the adherence task rather than eliminating adherence requirements [19,20]. They also fit the broader aging-HIV framework, in which comorbidity clustering, inflammation, frailty, and geriatric complexity require individualized treatment decisions rather than exclusion based on age or comorbidity count alone [21–25].

Several limitations should be acknowledged. This observational study did not include a contemporaneous oral ART comparator; therefore, it cannot determine whether outcomes would have differed with continued oral therapy. Residual selection is likely because clinicians may have offered CAB+RPV LA to patients considered suitable for scheduled attendance. Comorbidities were recorded from routine clinical data without uniform grading of severity, frailty, cognitive impairment, socioeconomic vulnerability, treatment control, or polypharmacy. Phenotypes and discontinuation reasons were nonmutually exclusive, event numbers were low for several endpoints, and follow-up beyond 25 months was limited.

In conclusion, comorbidity burden and multimorbidity identified older PWH with longer HIV histories and greater baseline clinical complexity, but we found no clear evidence that greater baseline comorbidity burden was associated with poorer virological durability, reduced adherence to scheduled injections, or lower persistence after switching to CAB+RPV LA. These findings do not establish equivalence or eliminate the need for individualized assessment. Rather, they suggest that comorbidity burden alone is an insufficient reason to avoid long-acting therapy, provided standard assessment confirms virological eligibility, resistance profile, drug-interaction risk, feasibility of injection attendance, safety monitoring needs, and patient preference. These data support the individualized use of CAB+RPV LA in selected PWH with comorbidities in routine care.

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Relativity Group: Complejo Asistencial de Ávila: Ana Cristina Antolí Royo, Carmen Grande Sáez, María Ángeles Garcinuño Jiménez; Complejo Asistencial de Segovia: Ana Carrero Gras, Eva María Ferreira Pasos; Complexo Hospitalario Universitario de Pontevedra: Hadrian Pernas Pardavila, Mercedes González, Nuria Vázquez Temprano; Hospital Central de la Defensa Gómez Ulla (Madrid): Miriam Estébanez, Tatiana Mata-Forte; Hospital Clínico San Carlos (Madrid): Ana Muñoz Gómez, José Reynaldo Homen Fernández, Juncal Pérez-Somarriba Moreno, Maravillas Carralón, María José Núñez Orantos, María Nieves Sanz Pérez, Noemí Cabello Clotet, Susana Olmedo Hernández, Valeria Cabral Sousa, Vicente Estrada, Virginia Víctor Palomares; Hospital Clínico Universitario de Valencia: Ana Ferrer Ribera, Andreu Belmonte, Carolina Pinto, María José Galindo Puerto, Rosa Oltra Sempere, Sandra Pérez Gómez; Hospital Clínico Universitario Lozano Blesa (Zaragoza): Álvaro Cecilio, Isabel Sanjoaquín Conde, María José Crusells Canales, Pilar Jiménez Marcen; Hospital Comarcal de la Vega Baja (Alicante): Ana Lucas Dato, Belén Martínez López, Inmaculada González Cuello, Jara Llenas García, María García López; Hospital Universitario de Burgos: Carolina Navarro, Luis Buzón, María Fernández; Hospital de Denia Marina Salud (Alicante): Amparo Exojo Morales, Carlos de Andrés David, Inmaculada Poquet Catalá, Karenina Antelo Cuéllar, Laia Navarro Peiró, María Josefa de la Asunción Villaverde, Silvia Lope Bolumar; Hospital de Jove (Asturias): Alba León Barbosa, Esther Nogales Nieves, Eva García Alcalde, Juan José Corte García, Lucía Alonso Alonso, María Vanessa López Peláez, Sara Jaber Carballo; Hospital de Santa Caterina de Salt (Girona): Albert

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Gómez Lozano, Sara García Torras; Hospital de Valls (Tarragona): Marta Milián Sanz; Hospital de Viladecans: Ana Isabel Lérida Urteaga, Antonia Pérez Barja, Javier López-Nieto Sempere, Magdalena Muelas Fernández; Hospital General Nuestra Señora del Prado (Castilla La Mancha): Beatriz de la Calle; Hospital General Universitario de Elche (Alicante): Ángela Botella Zaragoza, Félix Gutiérrez Rodero, Javier García Abellán, Mar Masiá, Paula Mascarell Arlandis, Sergio Padilla Urrea; Hospital General Universitario Gregorio Marañón (Madrid): Chiara Fanciulli, Cristina Diez Romero, Francisco Tejerina Picado, Juan Carlos López Bernaldo de Quirós, Leire Pérez Latorre, María Teresa Aldamiz-Echevarría Lois; Hospital General Universitario Morales Meseguer (Murcia): Antonio Jesús Sánchez Guirao; Hospital General Universitario Reina Sofía (Murcia): Ángeles Muñoz Pérez, Antonia Alcaraz García, Cristina Tomás Jiménez, Elena Guijarro Westermeyer, Enrique Bernal Morell, Eva García Villalba, Joaquín Bravo Urbieta, María Dolores Hernández Lorente, Rodrigo Martínez Rodríguez, Román González Hipólito; Hospital Obispo Polanco (Teruel): Noemí Ramos Vicente; Hospital Residencia Sant Camil de Sant Pere de Ribes (Barcelona): Patricia Barragán Gallo; Hospital Río Hortega de Valladolid: Alberto Juárez Toquero, Beatriz Valentín Casado, Jesica Abadía Otero, Julia Gómez Barquero, Pablo Bachiller Luque, Yolanda Arranz García; Hospital Universitario 12 de Octubre (Madrid): Adriana Pinto, David Rial, Federico Pulido, Juan Martín, Laura Bermejo Plaza, María De Lagarde, María Teresa López Caballero, Mireia Santacreu, Otilia Bisbal, Rafael Rubio, Roser Navarro, Victoria Macheño del Real; Hospital Universitario Álvaro Cunqueiro (Vigo): Celia Miralles Álvarez, Guillermo Pousada, Henar de las Heras Miralles, Luis Enrique Morano Amado; Hospital Universitario Central de Asturias: Víctor Asensi; Hospital Universitario Cruces (Vizcaya): Laura Guio Carrión, Mikel del Álamo; Hospital Universitario de Álava: Ester Sáez de Adana Arroniz, Juan Carlos Gainzarain Arana; Hospital Universitario de Alcorcón (Madrid): Ana Vegas Serrano, Juan Emilio Losa García, María Velasco Arribas; Hospital Universitario de Basurto (Bilbao): Maite Ganchegui Aguirre, Miriam López Martínez, Óscar Luis Ferrero Benítez; Hospital Universitario de Bellvitge (Barcelona): Alicia Sedo Mor, Juan Tiraboschi, Analuz Fernández; Hospital Universitario de Cabueñes (Asturias): Josefa Soler González, Víctor Arenas García; Hospital Universitario de Canarias: Lucia Romero, Nereyda Tosco García, Remedios Alemán Valls; Hospital Universitario de Fuenlabrada (Madrid): Guillermo Soria Fernández-Llamazares, Juan Víctor San Martín López, Ruth Calderón Hernáiz; Hospital Universitario de Guadalajara: Alberto Delgado Fernández, Lorenzo Sánchez, Miguel Torralba González de Suso; Hospital Universitario de Puerto Real (Cádiz): Alberto Romero Palacios; Hospital Universitario de Toledo: María Antonia Sepúlveda; Hospital Universitario de Torrejón (Madrid): Alejandra Gimeno García, Alejandro David Bendala Estrada, Carmen Montero Hernández, Diana Corps Fernández; Hospital Universitario de Vinalopó (Alicante): Jose Carlos Escribano, María del Mar García Navarro, Marouane Menchi Elanzi; Hospital Universitario Doctor José Molina Orosa (Las Palmas): Ana Cerezales Calviño, Bárbara Alonso Moreno, José Fernando Lluch Perales; Hospital Universitario Fundación Jiménez Díaz (Madrid): Alfonso Cabello, Miguel Górgolas Hernández-Mora; Hospital Universitario Infanta Elena (Madrid): María Rubio Olivera, Marta Clavero Olmos; Hospital Universitario Infanta Leonor (Madrid): Belén Escribano Losada, Guillermo Cuevas, Jesús Troya García, Mariano Matarranz, Pablo Ryan, Roberto Pedrero Tomé; Hospital Universitario La Paz (Madrid): Ana Belén Delgado Hierro, Carmen Busca, Jose Ignacio Bernardino, Juan González García, Luis Ramos Ruperto, Luz Martín Carbonero, María del Mar Arcos Rueda, María Eulalia Valencia, María Luisa Montes, Rafael Mican, Rocío Montejano; Hospital Universitario La Princesa (Madrid): Andoni Casen Gil, Ignacio de los Santos, María Aguilera García; Hospital Universitario Marqués de Valdecilla (Cantabria): Aitziber Illaro Uranga, Carlos Armiñanzas Castillo, Claudia González Rico, Francisco Arnaiz de las Revillas Almajano, Manuel Gutiérrez Cuadra, María Carmen Fariñas Álvarez, Noelia Ruiz Alonso; Hospital Universitario Miguel Servet (Zaragoza): Ángela Forcén Vicente de Vera, María Aranzazú Caudevilla Martínez, Rosa María Martínez Álvarez, Ruth Caballero Asensio; Hospital Universitario Mutua de Terrassa (Barcelona): David Dalmau Juanola, Laura Gisbert Pérez, Mireia Cairó Llobell, Roser Font Canals, Xavier Martínez Lacsa; Hospital Universitario Príncipe de Asturias (Madrid): José Sanz; Hospital Universitario Puerta de Hierro (Madrid): Alberto Díaz de Santiago, Ana Fernández Cruz, Sara de la Fuente Moral; Hospital Universitario Ramón y Cajal: Ana Moreno, Daniel de las Heras Gómez, María Jesús Pérez Elías, María Jesús Vivancos Gallego, Mario Pons Guillén; Hospital Universitario San Agustín (Asturias): Desiré Pérez Martínez, María Elisa Pino Diaz, Miguel Alberto de Zárraga Fernández; Hospital Universitario San Jorge (Huesca): Miguel Vicente Egido Murciano, Teresa Omiste Sanvicente; Hospital Universitario Son Espases (Palma de Mallorca): Adrián Ferré, Antoni Campins, Francisco Fanjul, Luisa Martín Pena, Melchor Riera; Hospital Universitario Son Llatzer (Palma de Mallorca): Adrián Rodríguez, Patricia Sorní Moreno; Hospital Universitario Virgen de las Nieves (Granada): Carmen Hidalgo; Sergio Sequera Arquelladas; Hospital Verge de la Cinta de Tortosa (Tarragona): Cristina Escrich; Parc Taulí Hospital Universitari (Sabadell): María del Carmen Navarro.

Author contributions: All authors collected and entered data from PWH at their respective institutions. J.T. and L. B. coordinated the cohort and supervised data curation. R.P.T. performed the statistical analyses. J.T. drafted the manuscript. All authors critically reviewed the manuscript and approved the final version.

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Data availability

The datasets used and/or analyzed in this study are available from the corresponding author upon reasonable request.

Conflicts of interest

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[a]Hospital Universitario Infanta Leonor, Madrid; [b]Hospital Universitario La Paz, IdiPaZ, CIBERINFEC, Madrid; [c]Hospital Clínico Universitario de Valencia, Valencia; [d]Hospital Universitario de Burgos, Burgos; [e]Hospital Universitario 12 de Octubre, Madrid; [f]Hospital Universitario de Canarias, Santa Cruz de Tenerife; [g]Hospital Universitario de Guadalajara. IDISCAM. Universidad de Alcalá, Madrid; [h]Hospital Universitario Puerta de Hierro, Madrid; [i]Hospital Universitario Son Espases, Palma de Mallorca; [j]Hospital Universitario Son Llatzer, Instituto de Investigación Sanitaria de les Illes Balears (IdISBa), Palma de Mallorca; [k]Hospital Universitario Fundación Jiménez Díaz, Instituto de Investigación Sanitaria Fundación Jiménez Díaz (IIS-FJD, UAM), Madrid; [l]Hospital Clínico Universitario Lozano Blesa, Zaragoza; [m]Hospital Universitario Parc Taulí, Barcelona; [n]Hospital Universitario La Princesa, Madrid; CIBERINFEC Instituto de Salud Carlos III, Madrid; [o]Hospital Universitario Virgen de las Nieves, Granada; [p]Hospital Universitario Álvaro Cunqueiro, Vigo; [q]Hospital Clínico San Cecilio, Granada; [r]Hospital de Denia Marina Salud, Alicante; [s]Hospital General Universitario Reina Sofía, Murcia; [t]Hospital Universitario Miguel Servet, Zaragoza; [u]Hospital Universitario de Puerto Real, Cádiz; [v]Hospital Universitario de Bellvitge, Barcelona; [w]Hospital Universitario de Torrejón, Madrid; [x]Complejo Asistencial Universitario de Segovia, Segovia; and [y]Hospital Universitario Fundación Alcorcón, Madrid, Spain.

Correspondence to Jesús Troya, MD, PhD, Hospital Universitario Infanta Leonor, Avenida Gran Vía Este 80, 28031 Madrid, Spain.
E-mail: jestrogar@hotmail.com

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Early patient-reported outcomes and planned persistence with lenacapavir for HIV preexposure prophylaxis in routine clinical care

Aniruddha Hazra[a,b], Ami Multani[c], Rona Vail[d], Stephen Sukumaran[d], Romini Smith[c], Drew Halbur[b] and Rupa R. Patel[e]

This multicenter study evaluated early patient-reported outcomes (PROs) among individuals initiating twice-yearly lenacapavir (LEN) for HIV preexposure prophylaxis (PrEP) in routine care. Convenience, driven by reduced dosing frequency, was the primary motivation for LEN initiation, and overall satisfaction was high despite frequent but generally mild injection-site reactions. Persistent nodules and pain emerged as the leading patient-reported concerns regarding future continuation, highlighting the importance of patient-centered counseling and implementation strategies to optimize long-term persistence with long-acting PrEP.

Long-acting injectable PrEP has the potential to overcome adherence challenges associated with daily oral PrEP. LEN, a first-in-class capsid inhibitor administered subcutaneously every 6 months, has demonstrated high efficacy for HIV prevention in registrational trials, with favorable safety profiles and high continuation rates [1–3]. However, little is known about how patients perceive LEN during early implementation in routine clinical care or which experiences may influence future persistence. Early PROs may provide insight into acceptability, tolerability, and potential barriers to sustained use during initial implementation [4]. We therefore evaluated early PROs among individuals initiating LEN PrEP across four U.S. community-based PrEP programs.

Individuals initiating LEN through December 31, 2025, were invited to complete a standardized REDCap survey after their first injection visit as part of a larger LEN implementation cohort [5]. Survey domains included motivations for choosing LEN, counseling regarding drug–drug interactions (DDIs), adherence to oral loading doses, injection site reactions (ISRs), satisfaction compared with previous PrEP modalities, anticipated LEN persistence, and an open-ended question regarding factors that might influence discontinuation. Analyses were descriptive, and open-text responses underwent thematic content analysis.

Among 96 individuals initiating LEN across four sites, 58 completed the survey (response rate 60.4%). Reduced dosing frequency was the most commonly cited reason for initiating LEN (82.8%), followed by difficulty remembering daily oral PrEP (32.8%). Most respondents (91.4%) reported receiving counseling regarding potential drug–drug interactions before initiation, and self-reported adherence to oral loading doses was high (98.2%).

Forty-five participants (77.5%) reported at least one ISR, most commonly pain (57.8%), swelling (44.4%), and nodules (37.8%). Despite their frequency, ISRs were generally well tolerated. Nearly two-thirds of participants (63.7%) described little or no interference with daily activities after their first injection visit, while six participants (10.3%) reported that ISRs bothered them "to a great extent." Overall satisfaction remained high, with 79.3% reporting greater satisfaction with LEN than with their previous PrEP regimen.

Since initiating LEN, 29 participants (50.0%) reported taking at least one concomitant medication or recreational substance, these included phosphodiesterase-5 (PDE-5) inhibitors (29.3%), other prescription medications (24.1%), and recreational substances (3.4%). Among those reporting concomitant medication or substance use, nine (31.0%) perceived a change in medication effects after starting LEN; all involved PDE-5 inhibitors.

Although satisfaction was high, seven participants (12.1%) reported that they did not plan to continue subsequent LEN injections and an additional two (3.4%) were unsure. No quantitative patient-reported factors were associated with anticipated discontinuation. Twenty-one participants provided open-text responses regarding factors that might influence future discontinuation (Fig. 1). ISRs were the most frequently identified theme (42.9%), particularly persistent nodules and pain. Several respondents described persistent nodules as cosmetically bothersome or affecting

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