

Supplementary Information For:

Immunometabolism is a key factor for the persistent spontaneous elite control of HIV-1 infection.

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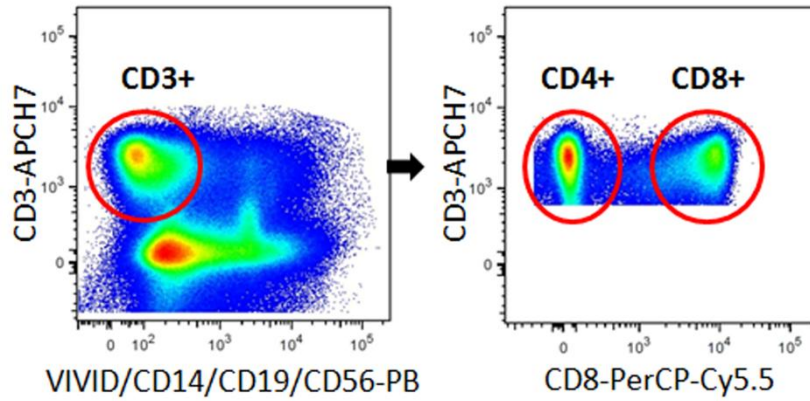
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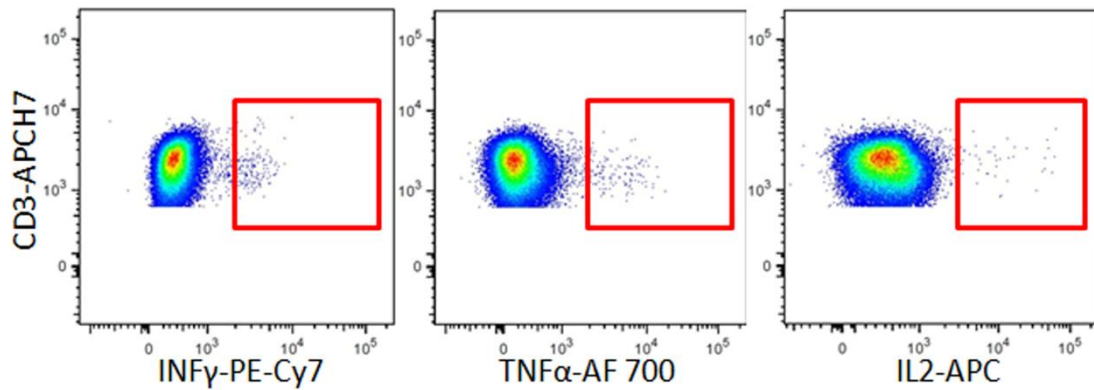
Annex I. Clinical Centres and research groups which contribute to ECRIS.

S1. SUPPLEMENTARY FIGURES

Supplementary Figure 1. Schematic diagram of the gating strategy.

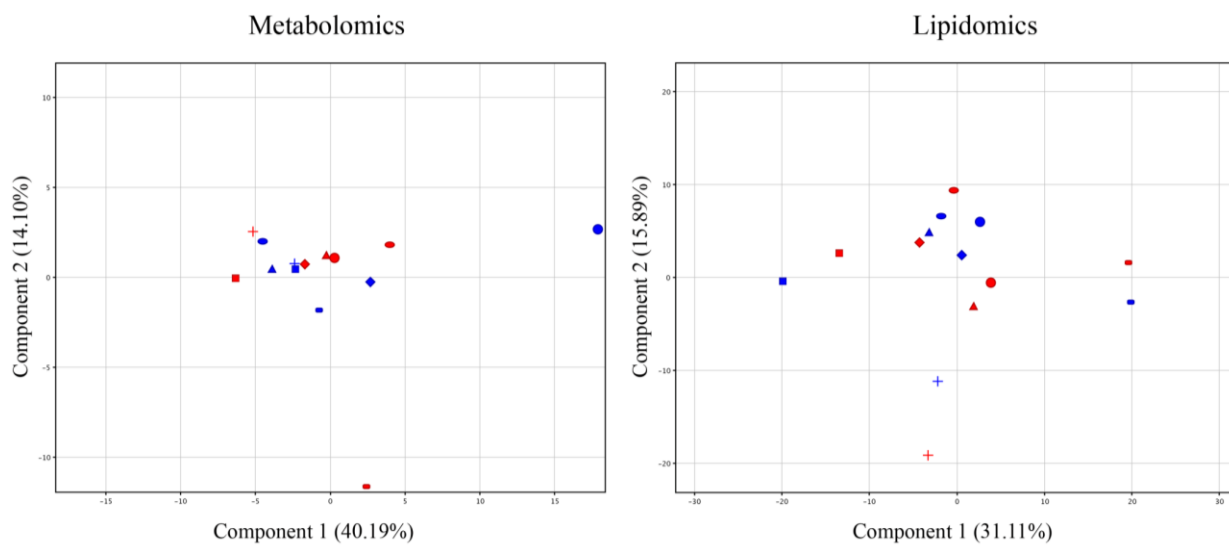


Cytokine production in CD4⁺
or CD8⁺ T-cell



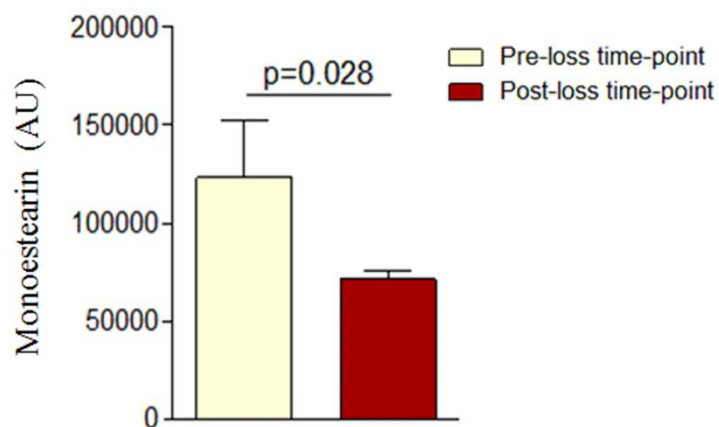
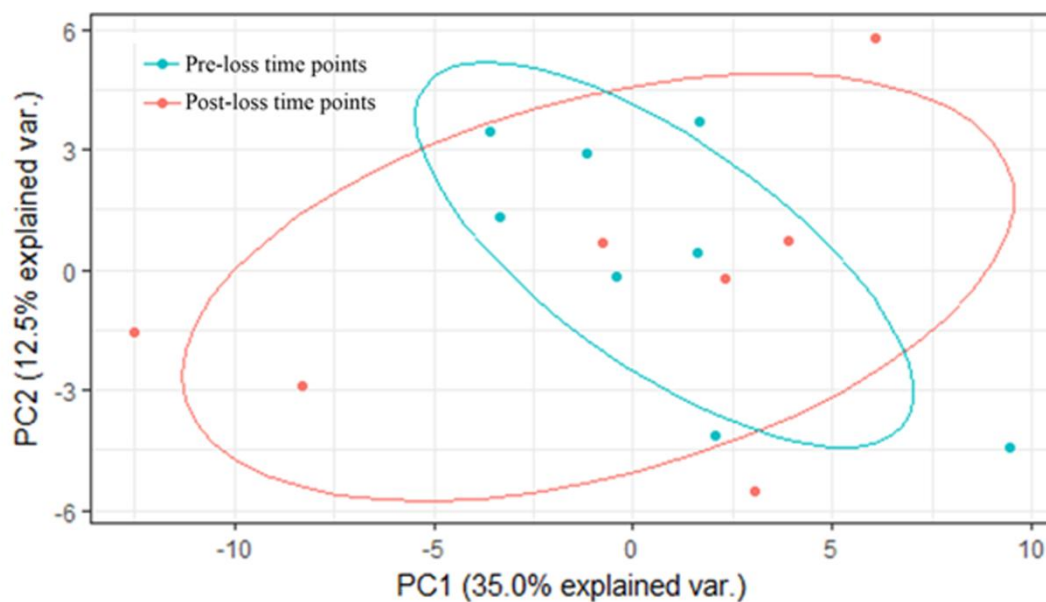
Representative plots showing the functional cytokine response to Gag peptides in CD4⁺ and CD8⁺ T-cells.

Supplementary Figure 2. PCA analysis for paired samples in PCs of the metabolomic and lipidomic approaches.



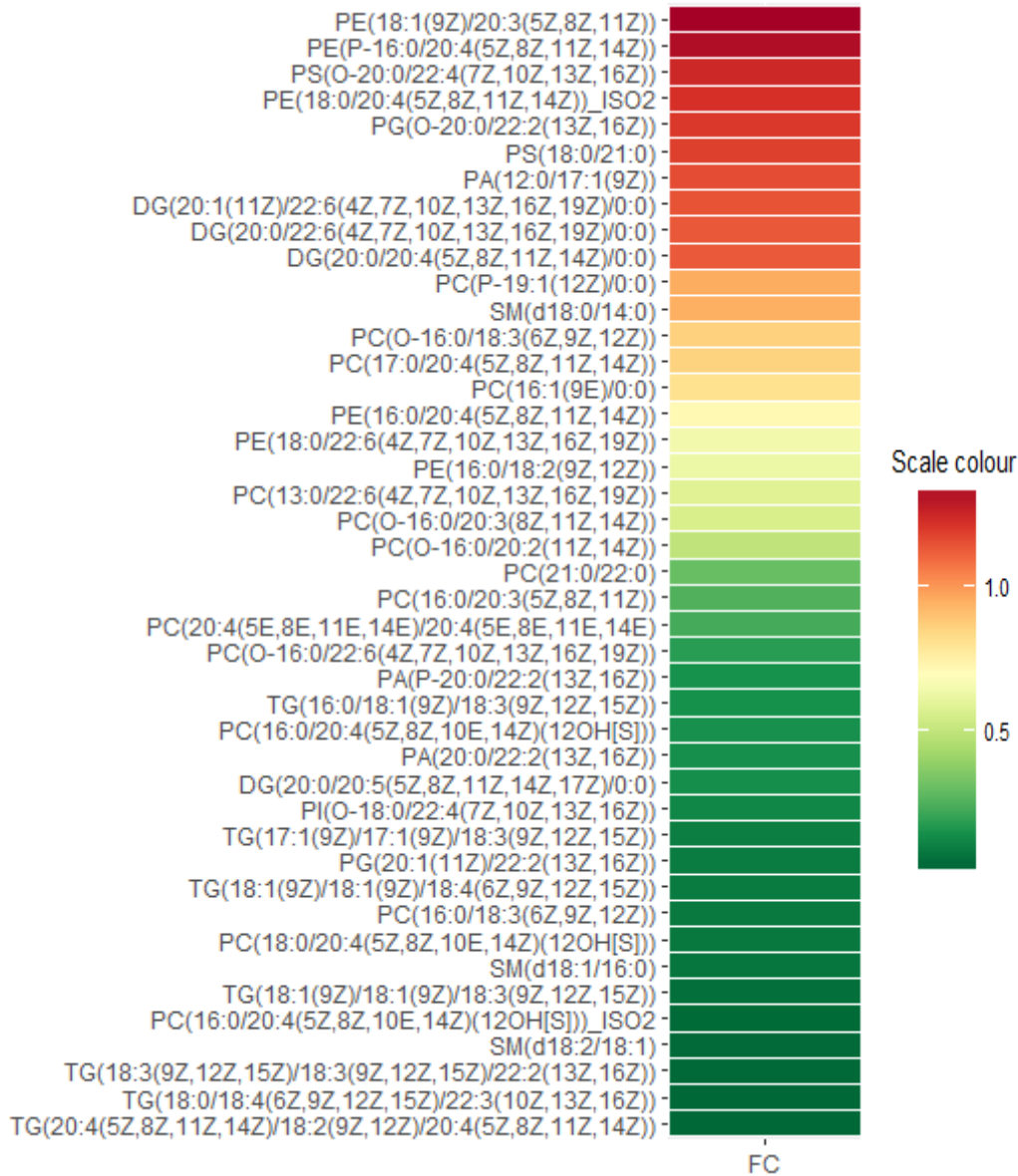
Each PC is represented by a different shape (n=8), and paired samples are represented in red and blue.

Supplementary Figure 3. Metabolomic analysis comparing TCs before and after the loss of control.



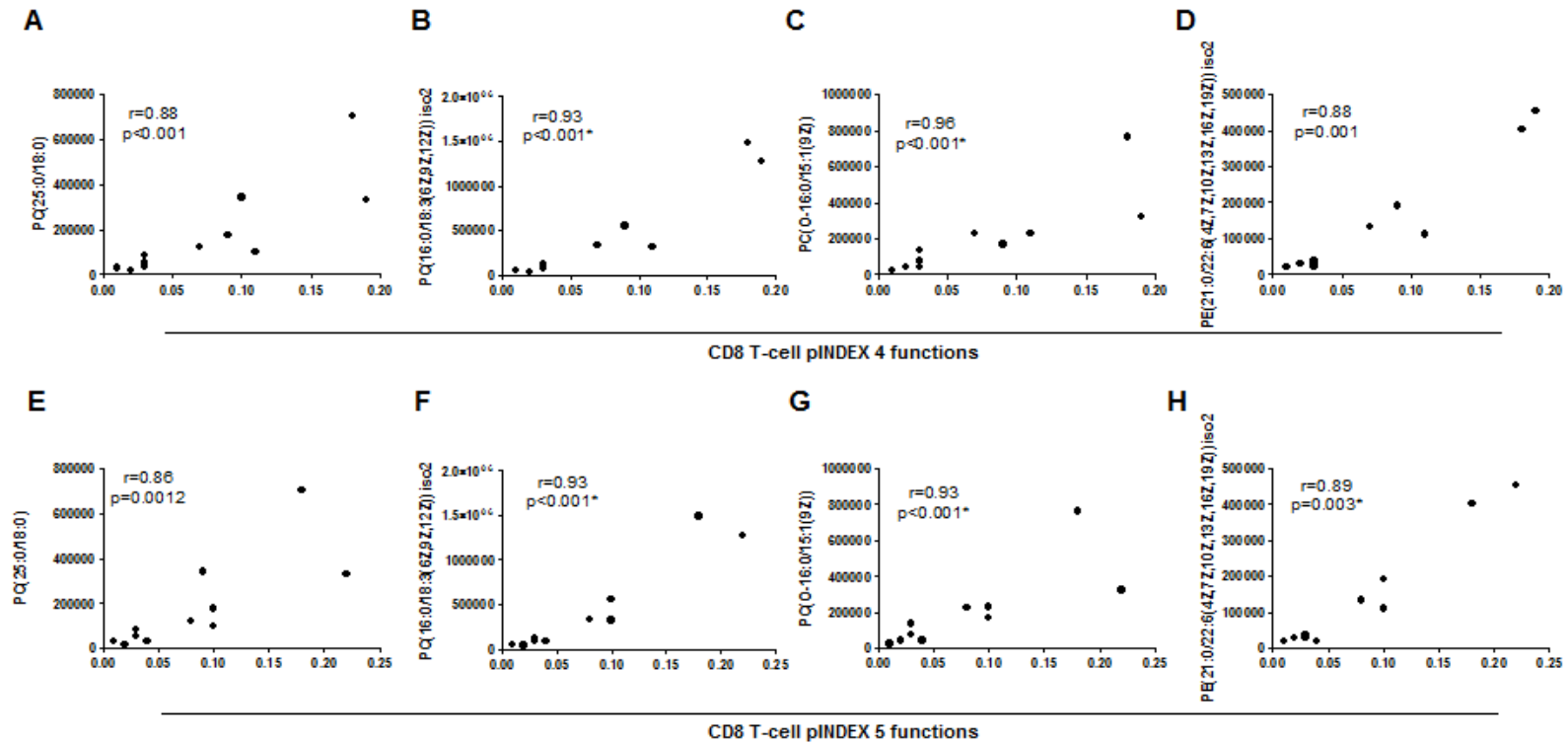
Score plot of the Principal Component Analysis (PCA) using all the analysed entities at pre-loss time points (blue, n=8) and post-loss time points (red, n=8) from TC (A). Monostearin was the only metabolite that was statistically significant different between TC pre-loss and post-loss time points (B).

Supplementary Figure 4. Changes in plasma lipid levels of transient controllers as effects of the loss of control.



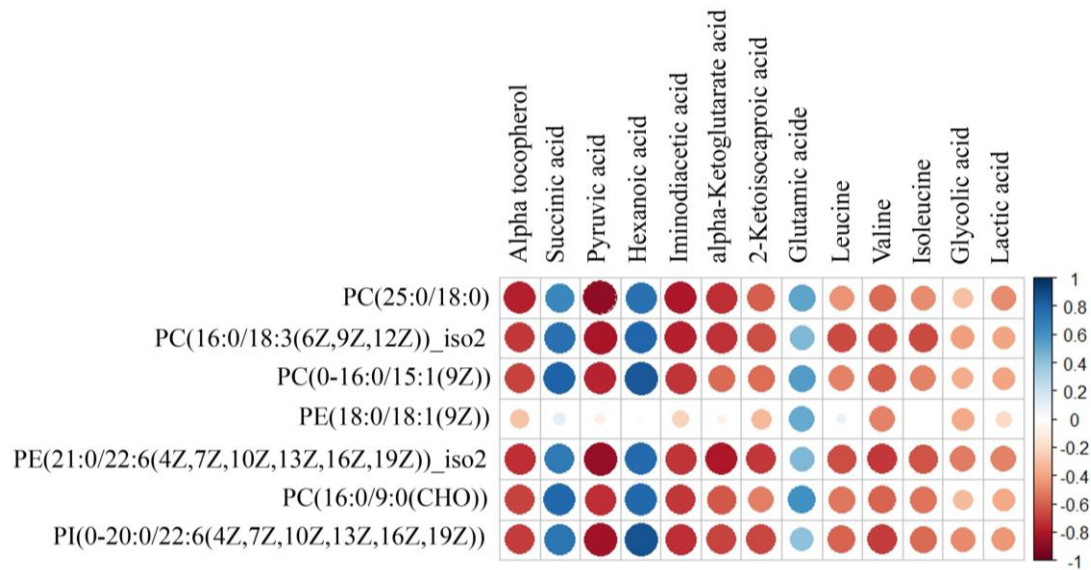
The fold change (FC) of each variable was calculated as 'A/B', where 'A' was the median value of or post-loss time points, and 'B' was median value of the pre-loss time points. The scale from green (low abundance) to red (high abundance) represents the normalized abundance in arbitrary units.

Supplementary Figure 5. Plasma lipid levels and Gag-specific polyfunctionality associations.



PC(25:0/18:0), PC(16:0/18:3(6Z,9Z,12Z)) iso2, PC(O-16:0/15:1(9Z)) and PE(21:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z)) iso2 plasma level correlations with four- and five- function Gag-specific CD8⁺ T-cell pINDEX from PCs and TCs before the loss of control (n=11). pINDEX based on the proportions of cells expressing combinations of IFN- γ , TNF- α and IL-2 plus CD107a (four functions) (A-D) and plus perforin (five functions) (E-H). Single and double production of CD107a and perforin were excluded from the analyses. An outlier (*) excluded from the analysis (n=10). The Spearman ρ correlation coefficient test was used.

Supplementary Figure 6. Associations between lipid and metabolite plasma levels.



The Spearman ρ correlation coefficient test was used. The scale from red (inversed associations) to blue (directed associations) represents the Spearman ρ correlation coefficient.

S2. SUPPLEMENTARY TABLES

Supplementary Table 1. Differentially plasma lipid levels comparing PC and TC before the loss of control.

Compound	FC	p-value
PA(20:0/22:2(13Z,16Z))	-33,583	0.010
PG(20:1(11Z)/22:2(13Z,16Z))_ISO1	-31,370	0.007
PI(O-18:0/22:4(7Z,10Z,13Z,16Z))	-29,104	0.007
PE(19:1(9Z)/22:2(13Z,16Z))	-17,404	<0.001
PA(P-20:0/22:2(13Z,16Z))_ISO1	-15,868	0.010
PI(O-20:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	-13,277	<0.001
DG(14:1(9Z)/18:2(9Z,12Z)/0:0)	-12,037	0.010
PC(16:0/9:0(CHO))	-11,650	0.001
PS(18:0/20:4(5Z,8Z,11Z,14Z))	-11,577	0.001
PI(22:1(11Z)/22:4(7Z,10Z,13Z,16Z))	-10,900	0.001
PE(21:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))_ISO1	-9,588	<0.001
PC(16:0/18:3(6Z,9Z,12Z))_ISO1	-9,089	<0.001
SM(d18:1/16:0)	-8,509	0.010
PC(16:0/22:6(4E,7E,10E,13E,16E,19E))	-7,943	0.009
PA(P-20:0/22:2(13Z,16Z))_ISO2	-7,684	<0.001
PC(25:0/18:0)	-7,313	<0.001
PC(20:4(5E,8E,11E,14E)/20:4(5E,8E,11E,14E))	-7,301	0.010
PC(16:0/20:3(5Z,8Z,11Z))_ISO1	-7,242	0.010
PS(18:2(9Z,12Z)/22:1(11Z))_ISO1	-7,241	0.004
TG(18:0/18:4(6Z,9Z,12Z,15Z)/22:3(10Z,13Z,16Z,19Z))	-7,023	0.038
TG(18:3(9Z,12Z,15Z)/20:4(5Z,8Z,11Z,14Z)/21:0)	-6,813	0.021
PG(P-20:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	-6,483	0.010
PE(18:0/18:1(9Z))	-6,244	0.017
PG(20:1(11Z)/22:2(13Z,16Z))_ISO2	-6,124	0.006
PC(O-16:0/15:1(9Z))	-5,439	<0.001
PE(21:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))_ISO2	-5,206	0.001
TG(16:0/18:1(9Z)/18:3(9Z,12Z,15Z))	-5,145	0.010
PC(16:0/20:4(5Z,8Z,10E,14Z)(12OH[S]))_ISO1	-5,136	0.010
DG(20:1(11Z)/20:5(5Z,8Z,11Z,14Z,17Z)/0:0)	-5,076	0.006
PC(O-16:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	-5,045	0.028
1-(8-[5]-ladderane-octanoyl)-2-(8-[3]-ladderane-octanyl)-sn-glycerophosphocholine	-5,022	0.010
TG(18:3(9Z,12Z,15Z)/21:0/22:5(7Z,10Z,13Z,19Z))	-4,751	0.029
TG(18:1(9Z)/18:1(9Z)/18:3(9Z,12Z,15Z))	-4,289	0.009
PC(16:0/18:3(6Z,9Z,12Z))_ISO2	-4,247	0.001
PA(13:0/16:0)	-4,103	0.008
GlcCer(d18:1/20:0)	-3,943	0.002
PC(16:0/20:4(5Z,8Z,10E,14Z)(12OH[S]))_ISO2	-3,758	0.010
PC(20:2(11Z,14Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	-3,445	0.042

PE(18:0/20:4(5Z,8Z,11Z,13E)(15Ke))	-3,300	0.021
PS(18:2(9Z,12Z)/22:1(11Z))_ISO2	-3,077	0.002
PA(15:0/18:4(6Z,9Z,12Z,15Z))	-3,072	0.050
PC(16:0/20:3(5Z,8Z,11Z))_ISO2	-3,055	0.010
2-(8-[3]-ladderane-octanyl)-sn-glycero-3-phosphoethanolamine	-3,049	0.010
PC(18:0/20:4(5Z,8Z,10E,14Z)(12OH[S]))_ISO1	-2,993	0.021
PC(18:0/20:4(5Z,8Z,10E,14Z)(12OH[S]))_ISO2	-2,777	0.001
DG(18:3(9Z,12Z,15Z)/20:0/0:0)	-2,764	0.010
DG(20:0/20:5(5Z,8Z,11Z,14Z,17Z)/0:0)	-2,634	0.010
PI(O-20:0/20:5(5Z,8Z,11Z,14Z,17Z))	-2,411	0.021
PS(P-20:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	-1,691	0.049
PI(18:4(6Z,9Z,12Z,15Z)/18:0)	-1,519	0.050
PC(P-19:1(12Z)/0:0)	1,105	0.001
PC(16:1(9E)/0:0)	1,176	0.021
PC(17:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))_ISO1	1,220	0.001
PC(O-20:0/22:4(7Z,10Z,13Z,16Z))	1,278	0.028
PC(16:0/20:3(5Z,8Z,11Z))_ISO3	1,281	0.050
PC(18:0/18:0)	1,287	0.038
PC(18:2(9Z,12E)/17:2(9Z,11E))	1,363	0.015
PC(15:0/18:2(9Z,12Z))	1,410	0.021
DG(20:0/22:5(7Z,10Z,13Z,16Z,19Z)/0:0)	1,449	0.010
DG(20:5(5Z,8Z,11Z,14Z,17Z)/22:0/0:0)	1,455	0.005
PC(16:1(9Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	1,466	<0.001
DG(20:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z)/0:0)	1,466	0.038
SM(d18:1/25:0)	1,519	0.028
PC(O-18:0/22:4(7Z,10Z,13Z,16Z))_ISO1	1,522	0.005
PC(15:0/20:5(5Z,8Z,11Z,14Z,17Z))	1,527	0.050
PE(16:0/18:2(9Z,12Z))	1,536	0.021
PC(O-18:0/22:5(4Z,7Z,10Z,13Z,16Z))	1,540	0.028
PC(16:0/22:5(4Z,7Z,10Z,13Z,16Z))	1,546	0.021
PC(O-18:0/22:4(7Z,10Z,13Z,16Z))_ISO2	1,583	0.038
PC(20:4(5E,8E,11E,14E)/20:4(5E,8E,11E,14E))_ISO1	1,584	0.010
PC(P-20:0/22:4(7Z,10Z,13Z,16Z))	1,592	0.010
PE(16:0/20:4(5Z,8Z,11Z,14Z))	1,593	0.021
TG(17:1(9Z)/18:1(9Z)/18:1(9Z))	1,596	0.021
PC(17:0/20:4(5Z,8Z,11Z,14Z))	1,614	0.015
PC(P-18:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	1,628	0.038
SM(d18:2/24:1)	1,699	0.007
PC(20:4(5E,8E,11E,14E)/20:4(5E,8E,11E,14E))_ISO2	1,700	0.001
PE(18:0/20:4(5Z,8Z,11Z,14Z))	1,707	0.010
PC(18:1(11Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))_ISO1	1,797	0.010
PC(O-18:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	1,814	0.007
TG(15:0/18:2(9Z,12Z)/18:2(9Z,12Z))	1,830	0.021
PC(16:0/20:5(5Z,8Z,11Z,14Z,17Z))	1,830	0.014
PC(O-20:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	1,832	<0.001

PC(15:1(9Z)/22:2(13Z,16Z))	1,852	0.003
PS(17:0/20:4(5Z,8Z,11Z,14Z))	1,870	0.028
TG(18:1(9Z)/18:2(9Z,12Z)/20:1(11Z))	1,882	0.038
PC(P-20:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	1,903	0.001
PC(18:1(11Z)/22:6(4Z,7Z,10Z,13Z,16Z,19Z))_ISO2	1,958	0.001
PE(18:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	2,009	0.003
PC(13:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))	2,021	0.003
TG(18:1(9Z)/18:2(9Z,12Z)/18:2(9Z,12Z))	2,041	0.015
TG(17:1(9Z)/18:1(9Z)/18:2(9Z,12Z))	2,209	0.01
PC(17:0/22:6(4Z,7Z,10Z,13Z,16Z,19Z))_ISO2	2,419	0.006

Diacylglycerides (DG), glucosylceramide (GlcCer), phosphatidic acid (PA), phosphatidylcholine (PC), phosphatidylethanolamine (PE), prostaglandin (PG) phosphatidylinositol (PI), sphingolipid (SM), phosphatidylserine (PS) and triacylglyceride (TG). FC, fold change.

S3. SUPPLEMENTARY INFORMATION

Annex I. Clinical Centers and research groups which contribute to ECRIS

Clinical centers:

Hospital Universitario de Valme (Sevilla): Juan Antonio Pineda, Eva Recio Sánchez, Fernando Lozano de León, Juan Macías, José Carlos Palomares, Manuel Parra, Jesús Gómez-Mateos.

Hospital General Universitario Santa Lucía (Cartagena): Onofre Juan Martínez-Madrid, Francisco Vera, Lorena Martínez.

Hospital Clinic de Barcelona (Barcelona): José M. Miró, Christian Manzardo, Laura Zamora, Iñaki Pérez, M^a Teresa García, Carmen Ligeró, José Luis Blanco, Felipe García-Alcaide, Esteban Martínez, Josep Mallolas, José M. Gatell.

Hospital General Universitario de Alicante (Alicante): Joaquín Portilla, Esperanza Merino, Sergio Reus, Vicente Boix, Livia Giner, Carmen Gadea, Irene Portilla, Maria Pampliega, Marcos Díez, Juan Carlos Rodríguez, Jose Sánchez-Payá.

Hospital Universitari de Bellvitge (Hospitalet de Llobregat): Daniel Podzamczer, Elena Ferrerm Arkaitz Imaz, Evan Van Den Eynde, Silvana Di Yacovo, Maria Sumoy.

Hospital Universitario de Canarias (Santa Cruz de Tenerife): Juan Luis Gómez, Patricia Rodríguez, María Remedios Alemán, María del Mar Alonso, María Inmaculada Hernández, Felicitas Díaz-Flores, Dácil García, Ricardo Pelazas.

Hospital Carlos III (Madrid): Vicente Soriano, Pablo Labarga, Pablo Barreiro, Pablo Rivas, Francisco Blanco, Luz Martín Carbonero, Eugenia Vispo, Carmen Solera.

Hospital Universitario Central de Asturias (Oviedo): Victor Asensi, Eulalia Valle, José Antonio Cartón.

Hospital Doce de Octubre (Madrid): Rafael Rubio, Federico Pulido, Mariano Matarranz, Maria Lagarde, Guillermo Maestro, Rafael Rubio-Martín.

Hospital Universitario Donostia (San Sebastián): José Antonio Iribarren, Julio Arrizabalaga, María José Aramburu, Xabier Camino, Francisco Rodríguez-Arrondo, Miguel Ángel von Wichmann, Lidia Pascual Tomé, Miguel Ángel Goenaga, M^a Jesús Bustinduy, Harkaitz Azkune Galparsoro. Maialen Iburguren, Mirian Aguado.

Hospital General Universitario de Elche (Elche): Félix Gutiérrez, Mar Masiá, Cristina López, Sergio Padilla, Andrés Navarro, Fernando Montolio, Catalina Robledano, Joan Gregori Colomé, Araceli Adsuar, Rafael Pascual, Federico Carlos, Maravillas Martínez.

Hospital Germans Trías i Pujol (Badalona): Roberto Muga, Jordi Tor, Arantza Sanvisens.

Hospital General Universitario Gregorio Marañón (Madrid): Juan Berenguer, Juan Carlos López Bernaldo de Quirós, Pilar Miralles, Isabel Gutiérrez, Margarita Ramírez, Belén Padilla, Paloma Gijón, Ana Carrero, Teresa Aldamiz-Echevarría, Francisco Tejerina, Francisco Jose Parras, Pascual Balsalobre, Cristina Diez.

Hospital Universitari de Tarragona Joan XXIII, IISPV, Universitat Rovira i Virgili (Tarragona): Francesc Vidal, Joaquín Peraire, Consuelo Viladés, Sergio Veloso, Montserrat Vargas, Miguel López-Dupla, Montserrat Olona, Alfonso Castellano, Verónica Alba, Esther Rodríguez-Gallego, Anna Rull.

Hospital Universitario La Fe (Valencia): Marta Montero, José Lacruz, Marino Blanes, Eva Calabuig, Sandra Cuellar, José López, Miguel Salavert.

Hospital Universitario La Paz/IdiPaz (Madrid): Juan González, Ignacio Bernardino de la Serna, José Ramón Arribas, María Luisa Montes, Jose M^a Peña, Blanca Arribas, Juan Miguel Castro, Fco Javier Zamora, Ignacio Pérez, Miriam Estébanez, Silvia García, Marta Díaz, Natalia Stella Alcáriz, Jesús Mingorance, Dolores Montero, Alicia González, Maria Isabel de José.

Hospital de la Princesa (Madrid): Ignacio de los Santos, Jesús Sanz, Ana Salas, Cristina Sarriá, Ana Gómez.

Hospital San Pedro-CIBIR (Logroño): José Antonio Oteo, José Ramón Blanco, Valvanera Ibarra, Luis Metola, Mercedes Sanz, Laura Pérez-Martínez.

Complejo Hospitalario de Navarra (Pamplona): María Rivero, Marina Itziar Casado, Jorge Alberto Díaz, Javier Uriz, Jesús Repáraz, Carmen Irigoyen, María Jesús Arraiza.

Hospital Parc Taulí (Sabadell): Ferrán Segura, María José Amengual, Gemma Navarro, Montserrat Sala, Manuel Cervantes, Valentín Pineda, Victor Segura, Marta Navarro, Esperanza Antón, M^a Merce Nogueras.

Hospital Ramón y Cajal (Madrid): Santiago Moreno, José Luis Casado, Fernando Dronda, Ana Moreno, María Jesús Pérez Elías, Dolores López, Carolina Gutiérrez, Beatriz Hernández, Nadia Madrid, Angel Lamas, Paloma Martí, Alberto de Diaz, Sergio Serrano, Lucas Donat.

Hospital Reina Sofía (Murcia): Alfredo Cano, Enrique Bernal, Ángeles Muñoz.

Hospital San Cecilio (Granada): Federico García, José Hernández, Alejandro Peña, Leopoldo Muñoz, Jorge Parra, Marta Alvarez, Natalia Chueca, Vicente Guillot, David Vinuesa, Jose Angel Fernández.

Centro Sanitario Sandoval (Madrid): Jorge Del Romero, Carmen Rodríguez, Teresa Puerta, Juan Carlos Carrió, Cristina González, Mar Vera, Juan Ballesteros.

Hospital Son Espases (Palma de Mallorca): Melchor Riera, María Peñaranda, María Leyes, M^o Angels Ribas, Antoni A Campins, Carmen Vidal, Leire Gil, Francisco Fanjul, Carmen Matinescu.

Hospital Universitario Virgen del Rocío (Sevilla): Manuel Leal, Pompeyo Viciano, Luis Fernando López-Cortés, Nuria Espinosa, Cristina Roca.

Research groups:

Hospital General Universitario Gregorio Marañón e Insituto de Investigación Sanitaria Gregorio Marañón. Maria Angeles Muñoz-Fernández, Jose Luis Jimenez, Daniel Sepúlveda, Rafael Ceña, Isabel García Merino, Irene Consuegra.

Hospital Clinic. Agathe León, Mireia Arnedo, Montse Plana, Nuria Climent, Felipe García.

Hospital Joan XXIII. Francesc Vidal, Joaquim Peraire, Consuelo Viladés, Esther Rodríguez-Gallego, Anna Rull, Verónica Alba.

IIS-Fundacion Jimenez Díaz, UAM. Jose Miguel Benito, Norma Rallón, Clara Restrepo, Marcial García, Alfonso Cabello, Miguel Gorgolas.

Centro Sandoval. Jorge Del Romero, Carmen Rodríguez, Mar Vera.

Fundacion IRSI CAIXA. José Esté, Esther Ballana, Miguel Angel Martinez, S Franco, María Nevot, Julia G Prado , Esther Jiménez

Hospital Ramón y Cajal. Alejandro Vallejo, Beatriz Sara Sastre, Santiago Moreno.

Virologia Molecular ISCIII. Maria Pernas, Concepción Casado, Cecilio López Galíndez

Infeccion viral e Inmunidad. ISCIII. Salvador Resino

Inmunopatología del SIDA. ISCIII. Laura Capa, Mayte Perez-Olmeda, Pepe Alcami

Mutacion y evolución de virus. Univ Valencia. Rafael Sanjuán, José Manuel Cuevas

Hospital Universitario Doce de Octubre (Madrid): Rafael Rubio, Federico Pulido, Otilia Bisbal, Asunción Hernando, Mariano Matarranz, María Lagarde, Lourdes Domínguez.

Universidad de la Laguna. Agustín Valenzuela-Fernández.

Hospital Virgen del Rocío: Ezequiel Ruiz-Mateos, Beatriz Dominguez-Molina, Laura Tarancón-Díez, María Reyes Jiménez-León, Mohamed Rafii-El-Idrissi Benhnia, Miguel Genebat, Manuel Leal, Pompeyo Viciano, Luis Fernando López-Cortés.