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High CD8 T cell percentage and HCV replication control are common features in HIV-1 controllers and HTLV-2-co-infected patients with a history of injection drug use

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ABSTRACT

HTLV-2/HIV-1-coinfected patients and HIV-infected patients with natural HIV-1 control show an immune capacity that allows some control of viral infections. These two groups of patients have showed an immune capacity that allows them to have some control over viral infections, very strong control of HIV-1 replication in the case of HIV-1 controllers. The purpose of this retrospective cross-sectional study was to compare viral and immunologic parameters between three cohorts of Caucasian adult HIV-1-infected patients, including HIV-1 controllers (29 patients), HTLV-2/HIV-1 chronic progressors (56 patients), and HIV-1 chronic progressors (101 patients), followed in two different tertiary University Hospitals in Spain.

Demographic parameters, nadir CD4 T cell count, CD4 and CD8 T cell counts and percentage, anti-HCV antibodies, HCV RNA load, HCV genotype, HIV-1 RNA loads, and anti-HTLV-2 antibodies were analyzed. HIV-1 controllers and HTLV-2/HIV-1 chronic progressors were younger and with shorter time since HIV-1 diagnosis compared to HIV-1 chronic progressors. HIV-1 controllers and HTLV-2/HIV-1 chronic progressors had significantly higher CD8 T cell percentage ($p = 0.002$ and $p = 0.016$, respectively) and lower levels of HCV RNA loads (0.015 and 0.007, respectively) compared to that of HIV-1 chronic progressors. Multivariate analyses showed that gender and HTLV-2 infection were independently associated to HCV RNA load, while only HTLV-2 infection was independently associated to CD8 T cell percentage. The implication of HTLV-2 infection in the control of HIV-1 and HCV infections is worth being further analyze.

1. Introduction

HTLV-2/HIV-1 co-infection is relatively frequent among injection drug users in North America and Western Europe since the 80´s (Abad et al., 2011; Beilke, 2012; Cooke et al., 2005; Roucoux and Murphy, 2004; Treviño et al., 2012). HTLV-2/HIV-1-coinfected patients have been reported to have lower levels of plasma HIV-1 RNA loads before antiretroviral treatment, and slower decrease of CD4 T cell counts (Abad-Fernández et al., 2015; Pilotti et al., 2013). Also, as previously reported by our group, HTLV-2/HIV-1-coinfected patients with HCV infection had decreased levels of transaminases and slower hepatic fibrosis development (Abad-Fernández et al., 2015).

Natural control of HIV-1 infection occurs in less than 1% of patients maintaining very low plasma HIV-1 RNA loads or even below the limit of detection, and usually with no clinical signs of disease progression for many years without any antiretroviral treatment (Boufassa et al., 2011; Lambotte et al., 2005; Madec et al., 2013; Okulicz and Lambotte, 2011). Viral characteristics such as mutations or deletions in viral

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proteins and host specific immunological and genetic determinants are related to natural suppression of viral replication (Betts et al., 2006; Boritz et al., 2016; Casado et al., 2013; Domínguez-Molina et al., 2017; Hunt et al., 2008; O'Connell et al., 2010; Okulicz et al., 2009; Ramirez et al., 2016; Sáez-Cirión et al., 2009; Vingert et al., 2012). On the other hand, higher frequency of spontaneous HCV clearance and lower plasma HCV RNA load have also been reported in HIV-1 controllers (Asher et al., 2014; Ruiz-Mateos et al., 2011; Sajidi et al., 2010).

These two groups of patients have showed an immune capacity that allows them to have some control over viral infections, very strong control of HIV-1 replication in the case of HIV-1 controllers. The aim of this study was to compare viral and immunologic parameters between HIV-1 controllers and HTLV-2/HIV-1 chronic progressors, in comparison with HIV-1 chronic progressors.

2. Methods

2.1. Patients

This was a retrospective, cross-sectional correlational study of HIV-1-infected individuals. All HTLV-2-infected patients included in this study were over 40 years, in line with the period in which intravenous drugs were frequently used in Spain, mostly among HIV-1-infected men (from the '80 s to the '90 s). These patients could have acquired HCV and HIV-1 co-infections by injection drug use (IDU) by the same time. In fact, almost all HTLV-2/HIV-1-infected patients diagnosed in the University Hospital Ramon y Cajal of Madrid were former IDU and were exposed to HCV. To avoid bias due to transmission route or HCV exposure, all the patients included in this study were former IDUs and with the presence of antibodies anti-HCV. Hence, three cohorts of Caucasian adult HIV-1 infected patients with a history of injection drug use followed in two different tertiary Hospitals in Spain, Virgen del Rocío University Hospital (Seville) and Ramón y Cajal University Hospital (Madrid), were included: a) 29 HIV-1 controllers with at least three consecutive plasma HIV-1 RNA load determinations below 2000 copies/mL (3.3 log HIV-1 RNA copies/mL) during at least 12 months in the absence of any antiretroviral therapy (Domínguez-Molina et al., 2016, León et al., 2016), and negative for anti-HTLV-2 antibodies; b) 56 HTLV-2/HIV-1-coinfected chronic progressors with at least 24 months of suppressive viremia under combination antiretroviral treatment (cART), with confirmed HTLV-2 infection, and with certainty that they never were HIV-1 controllers; and c) 101 HIV-1-infected chronic progressors, with at least 24 months of suppressive viremia under cART, negative for anti-HTLV-2 antibodies and with certainty that they never were HIV-1 controllers.

Among patients who received HCV treatment, only those who completed the treatment (pegylated IFN-alpha plus ribavirin during 48 weeks) more than one year before the inclusion in this study were included. This prevented the possible effect of the HCV treatment in the variables studied. All patients gave their written informed consent to participate in this study. The local ethics committee approved the study, which complied with the stipulations of the Declaration of Helsinki. Demographic parameters such as age, gender and route of HIV-1 infection transmission, as well as time since HIV-1 diagnosis and time on ART were collected.

2.2. Laboratory determinations

2.2.1. Serologic and virologic assays

Serum HIV antibodies were assayed by enzyme immunoassay (EIA, Abbott Laboratories, North Chicago, IL, USA), and reactive results were confirmed by western blot analysis (DuPont, Wilmington, DE, USA). Plasma HIV-1 RNA quantification was measured by quantitative polymerase chain reaction (qPCR, COBAS Ampliprep/COBAS Taqman HIV-1 test, Roche Molecular Systems, Basel, Switzerland) according to the manufacturer's protocol, with detection limit of 50 HIV-1 RNA copies/mL.

HCV antibodies were assayed by EIA (Siemens Healthcare Diagnosis, Malvern, Pennsylvania). Plasma HCV RNA quantification was measured by qPCR (COBAS Amplicor, Roche Diagnosis, Barcelona, Spain), and genotyped by line probe assay (Inno-Lipa HCV II, Bayer, Barcelona, Spain), following manufacturer´s instructions

HTLV antibodies were assayed in plasma samples using third generation Bioelisa HTLV-I + II 5.0 (Biokit, Barcelona, Spain) following manufacturer´s instructions, and repeatedly reactive results were confirmed using Inno-LIA HTLV-I/II Score (Fujirebio Diagnostics, Japan), that also discriminate between HTLV-1 and HTLV-2 infection. Also, in-house PCR for LTR, env and tax gene sequences performed in peripheral blood mononuclear cells (PBMC) was used to confirm the results (Abad et al., 2011).

2.2.2. T cell subsets

EDTA anticoagulated whole blood was processed to analyze $CD4^+$ and $CD8^+$ T cells by flow cytometry (FACScalibur, Becton Dickinson, Franklin Lanes, NJ, USA). Cells were stained with subtype-specific monoclonal antibodies, CD3, CD4, CD45 (TrueCount tubes, Becton Dickinson, Franklin Lanes, NJ, USA) to obtain the absolute numbers and percentajes. At least 10^5 $CD3^+$ T cells were collected for each sample and analyzed with by initially gating lymphocytes according to morphological parameters.

2.3. Statistical analysis

Continuous variables were expressed as median and interquartile range ($IQ_{25\text{-}75}$), and categorical variables were described by frequencies and proportions. The Mann-Whitney U test (non parametric) for independent samples was used to compare continuous variables. Differences between categorical variables were evaluated using contingency table (Chi square distribution). For continuous dependent variables (CD8 T cell percentage and HCV RNA load) univariate linear regression analysis was assessed using all variables studied. Those variables in the univariate analysis with $p < 0.1$ were included in the multivariate logistic regression analysis with stepwise enter method. The regression coefficient (β) and 95% confidence interval (CI) for β were estimated in this model. Variables were independently associated with the dependent variable when $p < 0.05$. Statistical analysis was performed using SPSS software 16.0 (SPSS Inc., Chicago, Illinois, USA).

3. Results and discussion

As show in Table 1, HIV-1 controllers and HTLV-2/HIV-1 chronic progressors were younger and with shorter time since HIV-1 diagnosis compared to HIV-1 chronic progressors. HTLV-2/HIV-1 chronic progressors had lower level of HIV RNA load compared to HIV-1 chronic progressors, according to previous reports (Abad-Fernández et al., 2015; Pilotti et al., 2013). Nadir CD4 T cell count was higher only in HIV-1 controllers. Interestingly, despite similar CD4 T cell count in the three groups of patients, HTLV-2/HIV-1 chronic progressors and HIV-1 controllers had higher levels of CD8 T cell percentage compared to that of HIV-1 chronic progressors (0.002 and 0.016, respectively), as show in Table 2. While HIV-1 controllers had higher CD4 T cell percentage compared to the that of the other two groups ($p = 0.005$ and $p = 0.029$, respectively), HTLV-2/HIV-1 chronic progressors showed higher levels of CD8 cell count ($p = 0.034$) and lower CD4/CD8 ratio compared to that of HIV-1 chronic progressors ($p = 0.020$), according to previously reported data (Abad-Fernández et al., 2015).

To analyse whether HCV infection could alters CD8 T cell percentage, only those patients with negative HCV RNA load (patients with sustained virological response and patients with spontaneous HCV clearance) were analyzed. In this case, HTLV-2/HIV-1 chronic progressors and HIV-1 controllers showed higher levels of CD8 T cell percentage compared to that of HIV-1 chronic progressors ($p = 0.041$ y

Table 1
Immunovirologic characteristics of the HCV-exposed injection drug users at study point.

N	HIV-1 controllers [1] 29	HTLV-2-HIV-1 chronic progressors [2] 56	1 vs 2 p	HIV-1 chronic progressors [3] 101	1 vs 3 p	2 vs 3 p
Age (years)	45 [39-49]	44 [42-49]	0.676	49 [45-52]	**0.002**	< **0.001**
Gender (male)	21 (72.4%)	42 (75%)	0.798	73 (72.3%)	0.988	0.713
Time since HIV-1 diagnosis (months)	224 [207-274]	250 [197-278]	0.723	264 [227-312]	**0.012**	**0.006**
Time on cART (months)	–	163 [141-195]	–	194 [153-234]	–	**0.001**
Suppressive cART (months)	–	58 [38-85]	–	108 [68-165]	–	< **0.001**
Time with natural HIV-1 control (months)	224 [197-274]	–	–	–	–	–
Zenith HIV load (log_{10} RNA copies/mL)	2.00 [1.57-2.92]	4.75 [4.30-5.27]	–	5.00 [4.71-5.60]	–	**0.005**
HCV infection						
Spontaneous clearance	5 (17.2 %)	9 (16.1 %)	0.809	4 (3.9 %)	**0.013**	**0.008**
HCV PCR positive	13 (44.8 %)	34 (60.7 %)	0.242	50 (49.5 %)	0.657	0.177
Sustained virological response (Peg IFN-α/RBV)	7 (24.1 %)	12 (21.4 %)	0.762	47 (46.5 %)	**0.031**	**0.002**
Unknown	4 (13.8%)	1 (1.8%)		–		
Zenith HCV load (log10 RNA IU/mL)	5.93 [5.44-6.52]	6.11 [5.56-6.89]	0.489	6.55 [6.25-6.93]	**0.007**	**0.015**
HCV genotypes						
Genotype 1	6 (20.7 %)	22 (39.3 %)	0.083	54 (53.5%)	**0.002**	0.088
Genotype 2	1 (3.4 %)	4 (7.1 %)	0.493	1 (1.0 %)	0.346	**0.003**
Genotype 3	8 (27.6 %)	9 (16.1 %)	0.201	18 (17.8 %)	0.248	0.787
Genotype 4	3 (10.3 %)	4 (7.1 %)	0.626	9 (8.9 %)	0.814	0.711
Unknown	11 (37.9%)	17 (30.4%)		19 (18.8%)		
Nadir CD4 T cell count (cells/mm^3)	392 [291-538]	125 [52-232]	< **0.001**	94 [47-179]	< **0.001**	0.260

Median and interquartile range (IQ_{25-75}) for continuous variables, and frequencies and proportions for categorical variables. Mann Whitney U test for continuous values and Fisher´s exact test (two tailed) for categorical values. cART, combined antiretroviral treatment. Significant when $p < 0.05$ in bold.

p = 0.044, respectively). In the same way, analyzing those patients with positive HCV RNA load at the time of the study, HTLV-2/HIV-1 chronic progressors and HIV-1 controllers also showed higher CD8 T cell percentage compared to that found in HIV-1 chronic progressors (See supplementary Table 1), although almost significant in this last group (p = 0.008 and p = 0.055, respectively).

To study the natural control of HCV replication among the three groups of patients, all available plasma HCV RNA load recorded before HCV treatment (including those patients who had sustained virological response at the time of the study) were included. Hence, both HIV-1 controllers and HTLV-2/HIV-1 chronic progressors had lower levels of plasma HCV RNA load compared to that of HIV-1 chronic progressors (p = 0.007 and p = 0.015, respectively), as shown in Table 1.

In contrast with our findings, higher HCV RNA loads were found in HCV/HIV-1/HTLV-2 and in HCV/HTLV-2-co-infected individuals among IDU from the USA (Hisada et al., 2005). On the other hand, HTLV-2 infection, regardless HIV-1 co-infection, appeared to reduce HCV RNA loads in a limited number of Brazilian patients (n = 5 with HIV-1 infection, and n = 8 with no HIV-1 infection) compared to HCV/HIV-1-co-infected patients (n = 548) (Alves et al., 2018), in agreement with our data. A possible explanation on these apparent discordant results might be the genetic background of the individuals and the circulating HTLV-2 strain. Indeed, HTLV-2 strains differ in these three countries, while HTLV-2a is mostly circulating in the USA, and HTLV-2c in Brazil, only HTLV-2b has been reported in Spain so far (Abad et al., 2011; Eiraku et al., 1996; Magri et al., 2013; Caterino-de-Araujo et al., 2018). HTLV-2a and HTLV-2b differ from HTLV-2c in an additional 25 amino acids at the C-terminal end of the protein Tax, which may have contributed to this discrepancy (Romanelli et al., 2013; Eiraku et al., 1996). Despite genotypic difference, HTLV-2c could be phenotypically more related to HTLV-2b, although this hypothesis requires further investigation.

Of notice, HCV genotype 1 was less represented in HIV-1 controllers (33.3%), that is in agreement with other reports (Sáez-Cirión et al., 2009), while the presence of this genotype was similar between HTLV-2/HIV-1 chronic progressors and HIV-1 chronic progressors. Also, HCV genotype 1 has been associated with high level of HCV RNA load (Rong et al., 2012). To prevent this bias in the analysis, only patients with HCV genotype 1 were analyzed. In this case, HCV RNA load was significantly lower in HTLV-2/HIV-1 chronic progressors (22 patients) compared to that of HIV-1 chronic progressors (53 patients), with statistical significance (p = 0.003) (See supplementary Table 2).

Table 2
Immunovirologic characteristics of the HCV-exposed injection drug users at study point.

N	HIV-1 controllers [1] 29	HTLV-2-HIV-1 chronic progressors [2] 56	1 vs 2 p	HIV-1 chronic progressors [3] 101	1 vs 3 p	2 vs 3 p
CD4 T cell count (cells/mm^3)			0.396		0.108	0.053
< 200	1 (3.45%)	3 (5.36%)		14 (13.8%)		
200-500	13 (44.8%)	27 (48.21%)		37 (36.6%)		
> 500	16 (55.2%)	26 (46.43%)		50 (49.5%)		
CD4 T cell percetage	31.7 [21.4-40.1]	23.9 [17.2-30.4]	**0.005**	25.7 [21.6-32.7]	**0.029**	0.159
CD8 T cell count (cells/mm^3)			0.416		0.275	**0.034**
< 500	4 (14.8%)	5 (8.93%)		18 (17.82%)		
500-1000	12 (44.4%)	26 (46.43%)		53 (52.47%)		
> 1000	11 (40.7%)	25 (44.64%)		30 (29.70%)		
CD8 T cell percentage	47.6 [41.3-56.6]	48.7 [38.3-57.7]	0.905	41.4 [33.2-49.4]	**0.004**	< **0.001**
CD4/CD8 ratio	0.72 [0.38-0.93]	0.49 [0.31-0.81]	0.071	0.62 [0.48-0.93]	0.710	**0.020**

Median and interquartile range (IQ_{25-75}) for continuous variables, and frequencies and proportions for categorical variables. Mann Whitney U test for continuous values and Fisher´s exact test (two tailed) for categorical values. cART, combined antiretroviral treatment, ART, antiretroviral treatment. * Including recorded HCV RNA load of those patients cured at study point before HCV treatment. Significant when $p < 0.05$ in bold.

Table 3
Factors independently associated with CD8 T cell percentage and HCV RNA load (dependent variables).

CD8 T cell percentage		HCV RNA load	
	Multivariate linear regression P value; β coefficient (95% CI)		Multivariate linear regression P value; β coefficient (95% CI)
Gender	NS	Age	NS
Zenith HIV-1 RNA load	NS	Gender	**0.014**; -0.377 [-0.675 - -0.079]
HIV-1 progressor	NS	Nadir CD4 count	NS
HIV-1 controller	NS	Spontaneous HCV clearance	NS
HTLV-2 infection	**0.009**; 6.461 [1.665-11.258]	HCV genotype 1	NS
		HCV genotype 4	NS
		HTLV-2 infection	**0.027**; -0.336 [-0.632 - -0.039]

Only variables with $p < 0.1$ in the univariant linear regression were analysed in the multivariate linear regression analysis. CI: confidence interval; NS, not significant. Significant when $p < 0.05$. NS, not significant.

Unfortunately, the same analysis including HIV-1 controllers had no statistical power because of the low number of patients (n = 5).

Gender was another possible bias; insomuch as lower levels of HCV RNA load has been associated with females (Rong et al., 2012). Among males, HCV RNA load was lower in both HTLV-2/HIV-1 chronic progressors (30 patients) and HIV-1 controllers (14 patients) compared to that of HIV-1 progressors (64 patients), with statistical significance ($p = 0.013$ and $p = 0.026$, respectively). The analysis including only females could not be performed due to the limited number of patients. Interestingly, spontaneous HCV clearance was more frequent in both HIV-1 controllers ($p = 0.013$), which is in accordance to elsewhere reported data comparing HIV-1/HCV-coinfected and HCV mono-infected patients (Sajidi et al., 2010; Jamalidoust et al., 2017; Soriano et al., 2008; Berger et al., 1996; Rong et al., 2012), and HTLV-2/HIV-1 chronic progressors ($p = 0.008$) compared to that found among HIV-1 chronic progressors, as shown in Table 1. Nevertheless, HCV genotype 1 has been associated with higher levels of HCV spontaneous clearance (Mangia et al., 2013; Grebely et al., 2014; Marcellin et al., 2015). In this study, HCV genotype 1 was less represented in HIV-1 controllers but they had higher rate of spontaneous clearance. Perhaps other factors (genetic factors and others) could give account for this apparent discrepancy (Thomas et al., 2009). In the case of HTLV-2 co-infected patients, with no differences regarding HCV genotype 1 compared to progressors, HTLV-2 infection itself might have a singular role, in combination with the above mentioned host genetic factors.

To evaluate which factors were independently associated with HCV RNA load and CD8 T cell percentage (as dependent variables), all variables with $p < 0.1$ in the univariate analysis were included in the multivariate logistic regression test. Hence, gender and HTLV-2 infection were independently associated with HCV RNA load, while HTLV-2 infection were independently associated with CD8 T cell percentage, as shown in Table 3. These findings show the importance of the HTLV infection in the improvement of the immune system against viral infections.

This study had a number of limitations that has to be acknowledged, such as the low number of elite controllers (< 50 copies HIV-1 RNA per mL) that did not allow statistical powered comparisons with viremic controllers (< 2000 copies HIV-1 RNA per mL). In addition, it must take into account that HIV-1 controllers were not under antiretroviral treatment, contrary to the other two groups of patients.

The implication of HTLV-2 infection in the control of HIV-1 and HCV infections is worth being further analyze. Factors such as Tax-2 protein has a potential to induce cytokine gene expression such as interferon or MIP-1a (Beilke, 2012), and the antisense protein APH-2 play key roles in the virus lifecycle and persistence in the host inhibiting HIV-1 transcription (Murphy et al., 2016). Characteristics such as genetic determinants of the immune response, cytotoxic CD8 T lymphocyte response, CD4 T cell response and humoral response, among others, have to be further studied to determine the role of HTLV-2 against viral infections.

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Conflict of interest

None to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.virusres.2019.02.007.

References

Abad, M., Dronda, F., Domínguez, E., Moreno, S., Vallejo, A., 2011. HTLV-2b among HIV-1-coinfected injecting drug users in Spain. AIDS Res. Hum. Retroviruses 27, 579–583.
Abad-Fernández, M., Moreno, A., Dronda, F., del Campo, S., Quereda, C., Casado, J.L., Pérez-Elías, M.J., Moreno, S., Vallejo, A., 2015. Delayed liver fibrosis in HTLV-2-infected patients co-infected with HIV-1 and hepatitis C virus with suppressive antiretroviral therapy. AIDS 29, 401–409.
Alves, F.A., Campos, K.R., Lemos, M.F., Moreira, R.C., Caterino-de-Araujo, A., 2018. Hepatitis C viral load in HCV-monoinfected and HCV/HIV-1-, HCV/HTLV-1/-2-, and HCV/HIV/HTLV-1/-2-co-infected patients from São Paulo, Brazil. Braz. J. Infect. Dis. 22, 123–128.
Asher, A.K., Santos, G.M., Evans, J., Dokubo, E.K., Lee, T.H., Martin, J.N., Deeks, S.G., Tobler, L.H., Busch, M., Hunt, P.W., Page, K., 2014. A closer look at hepatitis C clearance in HIV controllers: a response. AIDS 28, 1241–1242.
Beilke, M.A., 2012. Retroviral coinfections: HIV and HTLV: taking stock of more than a quarter century of research. AIDS Res. Hum. Retroviruses 28, 139–147.
Berger, A., von Depka Prondzinski, M., Doerr, H.W., Rabenau, H., Weber, B., 1996. Hepatitis C plasma viral load is associated with HCV genotype but not with HIV coinfection. J. Med. Virol. 48, 339–343.
Betts, M.R., Nason, M.C., West, S.M., De Rosa, S.C., Migueles, S.A., Abraham, J., Lederman, M.M., Benito, J.M., Goepfert, P.A., Connors, M., Roederer, M., Koup, R.A., 2006. HIV nonprogressors preferentially maintain highly functional HIV-specific CD8+ T cells. Blood 107, 4781–4789.
Boritz, E.A., Darko, S., Swaszek, L., Wolf, G., Wells, D., Wu, X., Henry, A.R., Laboune, F., Hu, J., Ambrozak, D., Hughes, M.S., Hoh, R., Casazza, J.P., Vostal, A., Bunis, D., Nganou-Makamdop, K., Lee, J.S., Migueles, S.A., Koup, R.A., Connors, M., Moir, S., Schacker, T., Maldarelli, F., Hughes, S.H., Deeks, S.G., Douek, D.C., 2016. Multiple

origins of virus persistence during natural control of HIV infection. Cell 166, 1004–1015.
Boufassa, F., Saez-Cirion, A., Lechenadec, J., Zucman, D., Avettand-Fenoel, V., Venet, A., Rouzioux, C., Delfraissy, J.F., Lambotte, O., Meyer, L., ANRS EP36 HIV Controllers Study Group, 2011. CD4 dynamics over a 15 year-period among HIV controllers enrolled in the ANRS French observatory. PLoS One 6, e18726.
Casado, C., Pernas, M., Sandonis, V., Alvaro-Cifuentes, T., Olivares, I., Fuentes, R., Martínez-Prats, L., Grau, E., Ruiz, L., Delgado, R., Rodríguez, C., del Romero, J., López-Galíndez, C., 2013. Identification of a cluster of HIV-1 controllers infected with low replicating viruses. PLoS One 8, e77663.
Caterino-de-Araujo, A., Alves, F.A., Campos, K.R., Lemos, M.F., Moreira, R.C., 2018. Making the invisible visible: searching for human T-cell lymphotropic virus types 1 and 2 (HTLV-1 and HTLV-2) in patients with viral hepatitis B and C in Brazil. Mem. Inst. Oswaldo Cruz, Rio de Janeiro 113, 130–134.
Cooke, F.J., Geretti, A.M., Zuckerman, M., 2005. Human T-cell lymphotropic virus antibody prevalence in HIV-1-infected individuals attending a sexual health clinic in South-East London. J. Med. Virol. 76, 143–145.
Domínguez-Molina, B., León, A., Rodríguez, C., Benito, J.M., Lopez-Galindez, C., Garcia, F., Del Romero, J., Gutierrez, F., Viciana, P., Alcami, J., Leal, M., Ruiz-Mateos, E., 2016. Analysis of non-AIDS-defining events in HIV controllers. Clin. Infect. Dis. 62, 1304–1309.
Domínguez-Molina, B., Tarancón-Díez, L., Hua, S., Abad-Molina, C., Rodriguez-Gallego, E., Machmach, K., Vidal, F., Tural, C., Moreno, S., Goñi, J.M., Ramírez de Arellano, E., Del Val, M., Gonzalez-Escribano, M.F., Del Romero, J., Rodriguez, C., Capa, L., Viciana, P., Alcamí, J., Yu, X.G., Walker, B.D., Leal, M., Lichterfeld, M., Ruiz-Mateos, E., ECRIS integrated in the Spanish AIDS Research Network, 2017. HLA-B*57 and IFNL4-related polymorphisms are associated with protection against HIV-1 disease progression in controllers. Clin. Infect. Dis. 64, 621–628.
Eiraku, N., Novoa, P., Ferreira, M.C., Monken, C., Ishak, R., da Costa Ferreira, O., Zhu, S.W., Lorenco, R., Ishak, M., Azvedo, V., Guerreiro, J., de Oliveira, M.P., Loureiro, P., Hammerschlak, N., Ijichi, S., Hall, W.M., 1996. Identification and characterization of a new and distinct molecular subtype of human T-cell lymphotropic virus type 2. J. Virol. 70, 1481–1492.
Grebely, J., Page, K., Sacks-Davis, R., van der Loeff, M.S., Rice, T.M., Bruneau, J., Morris, M.D., Hajarizadeh, B., Amin, J., Cox, A.L., Kim, A.Y., McGovern, B.H., Schinkel, J., George, J., Shoukry, N.H., Lauer, G.M., Maher, L., Lloyd, A.R., Hellard, M., Dore, G.J., Prins, M., InC3 Study Group, 2014. The effects of female sex, viral genotype and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection. Hepatology 59, 109–120.
Hisada, M., Chatterjee, N., Kalaylioglu, Z., Battjes, R.J., Goedert, J.J., 2005. Hepatitis C virus load and survival among injection drug users in the United States. Hepatology 42, 1446–1452.
Hunt, P.W., Brenchley, J., Sinclair, E., McCune, J.M., Roland, M., Page-Shafer, K., Hsue, P., Emu, B., Krone, M., Lampiris, H., Douek, D., Martin, J.N., Deeks, S.G., 2008. Relationship between T cell activation and CD4+ T cell count in HIV-seropositive individuals with undetectable plasma HIV RNA levels in the absence of therapy. J. Infect. Dis. 197, 126–133.
Jamalidoust, M., Namayandeh, M., Moghadami, M., Ziyaeyan, M., 2017. Comparison of HCV viral load and its genotype distributions in HCV mono- and HIV/HCV co-infected illicit drug users. Virol. J. 14, 127.
Lambotte, O., Boufassa, F., Madec, Y., Nguyen, A., Goujard, C., Meyer, L., Rouzioux, C., Venet, A., Delfraissy, J.F., SEROCO-HEMOCO Study Group, 2005. HIV controllers: a homogeneous group of HIV-1-infected patients with spontaneous control of viral replication. Clin. Infect. Dis. 41, 1053–1056.
León, A., Pérez, I., Ruiz-Mateos, E., Benito, J.M., Leal, M., Lopez-Galindez, C., Rallon, N., Alcami, J., Lopez-Aldeguer, J., Viciana, P., Rodriguez, C., Grau, E., Iribarren, J., Gatell, J.M., Garcia, F., EC and Immune Pathogenesis Working group of the Spanish AIDS Research Network, 2016. Rate and predictors of progression in elite and viremic HIV-1 controllers. AIDS 30, 1209–1220.
Madec, Y., Boufassa, F., Porter, K., Prins, M., Sabin, C., d'Arminio Monforte, A., Amornkul, P., Bartmeyer, B., Sannes, M., Venet, A., Lambotte, O., Meyer, L., CASCADE Collaboration in Eurocoord, 2013. Natural history of HIV-control since seroconversion. AIDS 27, 2451–2460.
Magri, M.C., Brigido, L.F.M., Morimoto, H.K., Caterino-de-Araujo, A., 2013. HTLV type 2a strains among HIV-1-coinfected patients from Brazil have originated mostly from Brazilian Amerindians. AIDS Res. Hum. Retroviruses 29, 1010–1018.
Mangia, A., Santoro, R., Copetti, M., Massari, M., Piazzolla, V., Spada, E., Cappucci, G., Missale, G., Mottola, L., Agostinacchio, E., Mauro, L., Zuccaro, O., Maio, P., Pellegrini, F., Folgori, A., Ferrari, C., 2013. Treatment optimization and prediction of HCV clearance in patients with acute HCV infection. J. Hepatology 59, 221–228.
Marcellin, F., Demoulin, B., Spire, B., Suzan-Monti, M., Roux, P., Protopopescu, C., Sagaon-Teyssier, L., Duracinsky, M., Dray-Spira, R., Carrieri, M.P., ANRS-VESPA2 Study Group, 2015. Spontaneous and post-treatment HCV clearance: relationships with health-related quality of life in HIV infection (ANRS-VESPA2 study). Expert Rev. Gastroenterol. Hepatol. 9, 701–713.
Murphy, J., Hall, W.W., Ratner, L., Sheehy, N., 2016. Novel interactions between the HTLV antisense proteins HBZ and APH-2 and the NFAR protein family: implications for the HTLV lifecycles. Virology 494, 129–142.
O'Connell, K.A., Brennan, T.P., Bailey, J.R., Ray, S.C., Siliciano, R.F., Blankson, J.N., 2010. Control of HIV-1 in elite suppressors despite ongoing replication and evolution in plasma virus. J. Virol. 84, 7018–7028.
Okulicz, J.F., Lambotte, O., 2011. Epidemiology and clinical characteristics of elite controllers. Curr. Opin. HIV AIDS 6, 163–168.
Okulicz, J.F., Marconi, V.C., Landrum, M.L., Wegner, S., Weintrob, A., Ganesan, A., Hale, B., Crum-Cianflone, N., Delmar, J., Barthel, V., Quinnan, G., Agan, B.K., Dolan, M.J., Infectious Disease Clinical Research Program (IDCRP) HIV Working Group, 2009. Clinical outcomes of elite controllers, viremic controllers, and long-term non-progressors in the US Department of Defense HIV natural history study. J. Infect. Dis. 200, 1714–1723.
Pilotti, E., Bianchi, M.V., De María, A., Bozzano, F., Romanelli, M.G., Bertazzoni, U., Casoli, C., 2013. HTLV-1/-2 and HIV-1 co-infections: retroviral interference on host immune status. Front. Microbiol. 4, 372.
Ramirez, C.M., Sinclair, E., Epling, L., Lee, S.A., Jain, V., Hsue, P.Y., Hatano, H., Conn, D., Hecht, F.M., Martin, J.N., McCune, J.M., Deeks, S.G., Hunt, P.W., 2016. Immunologic profiles distinguish aviremic HIV-infected adults. AIDS 30, 1553–1562.
Romanelli, M.G., Diani, E., Bergamo, E., Casoli, C., Ciminale, V., Bex, F., Bertazzoni, U., 2013. Highlights on distinctive structural and functional properties of HTLV Tax proteins. Front. Microbiol. 4, 271.
Rong, X., Lu, L., Wang, J., Xiong, H., Huang, J., Chen, J., Huang, K., Xu, R., Wang, M., Zhang, X., Guo, T., Liu, Y., Gao, G., Fu, Y., Nelson, K.E., 2012. Correlation of viral loads with HCV genotypes: higher levels of virus were revealed among blood donors infected with 6a strains. PLoS One 7, e52467.
Roucoux, D., Murphy, E., 2004. The epidemiology and disease outcomes of HTLV-2. AIDS Res. Hum. Retroviruses 61, 144–154.
Ruiz-Mateos, E., Machmach, K., Romero-Sánchez, M.C., Ferrando-Martinez, S., Viciana, P., Del Val, M., Muñoz-Fernandez, M.A., Genebat, M., Leal, M., Cohort of the Spanish AIDS Research Network, 2011. Hepatitis C virus replication in Caucasian HIV controllers. J. Viral Hepat. 18, e350–7.
Sáez-Cirión, A., Sinet, M., Shin, S.Y., Urrutia, A., Versmisse, P., Lacabaratz, C., Boufassa, F., Avettand-Fènoël, V., Rouzioux, C., Delfraissy, J.F., Barré-Sinoussi, F., Lambotte, O., Venet, A., Pancino, G., ANRS EP36 HIV Controllers Study Group, 2009. Heterogeneity in HIV suppression by CD8 T cells from HIV controllers: association with Gag-specific CD8 T cell responses. J. Immunol. 182, 7828–7837.
Sajidi, M.M., Shakeri, N., Talwani, R., Redfield, R.R., 2010. Hepatitis C infection in HIV-1 natural viral suppressors. AIDS 24, 1689–1695.
Soriano, V., Mocroft, A., Rockstroh, J., Ledergerber, B., Knysz, B., Chaplinskas, S., Peters, L., Karlsson, A., Katlama, C., Toro, C., Kupfer, B., Vogel, M., Lundgren, J., EuroSIDA Study Group, 2008. Spontaneous viral clearance, viral load, and genotype distribution of hepatitis C virus (HCV) in HIV-infected patients with anti-HCV antibodies in Europe. J. Infect. Dis. 198, 1337–1344.
Thomas, D.L., Thio, C.L., Martin, M.P., Qi, Y., Ge, D., O'Huigin, C., Kidd, J., Kidd, K., Khakoo, S.I., Alexander, G., Goedert, J.J., Kirk, G.D., Donfield, S.M., Rosen, H.R., Tobler, L.H., Busch, M.P., McHutchison, J.G., Goldstein, D.B., 2009. Carrington M. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature 461, 798–801.
Treviño, A., Aguilera, A., Caballero, E., Benito, R., Parra, P., Eiros, J.M., Hernandez, A., Calderón, E., Rodríguez, M., Torres, A., García, J., Ramos, J.M., Roc, L., Marcaida, G., Rodríguez, C., Trigo, M., Gomez, C., de Lejarazu, R.O., de Mendoza, C., Soriano, V., HTLV Spanish Study Group, 2012. Trends in the prevalence and distribution of HTLV-1 and HTLV-2 infections in Spain. Virol. J. 9, 71.
Vingert, B., Benati, D., Lambotte, O., de Truchis, P., Slama, L., Jeannin, P., Galperin, M., Perez-Patrigeon, S., Boufassa, F., Kwok, W.W., Lemaître, F., Delfraissy, J.F., Thèze, J., Chakrabarti, L.A., 2012. HIV controllers maintain a population of highly efficient Th1 effector cells in contrast to patients treated in the long term. J. Virol. 86, 10661–10674.