RECENTLY ACQUIRED HEPATITIS C: EPIDEMIOLOGICAL CHARACTERISTICS AND TREATMENT RESPONSE IN A LARGE COHORT OF MSM LIVING WITH HIV IN MADRID

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Title page

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Title: *Recently acquired hepatitis C: Epidemiological characteristics and treatment response in a large cohort of MSM living with HIV in Madrid*

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Abstract

Introduction: We analyzed epidemiological, clinical characteristics, and the response to treatment in people living with HIV (PLHIV) who recently acquired hepatitis C (RAHC) in a multicentre study in Madrid (Spain).

Methods: Multicenter, ambispective, observational study of RAHC in men who have sex with men (MSM) infected with HIV. Clinical, epidemiological, and RAHC evolution were recorded prospectively in 2019 and 2020 and retrospectively in 2017 and 2018. In patients who received HCV treatment, sustained virological response (SVR) was provided 12 weeks after the end of treatment in an intention to treat analysis (ITT): all treated patients were included; and in analysis per-protocol (PP): missing patients were excluded.

Results: Overall, 133 patients were included. Median (IQR) age was 40 (34.3–46.1) years, 90.9% had at least one previous sexual transmission disease (STD), and 33.6% had previously hepatitis C. More than half of the prospective sample included patients using chemsex related drugs (57.3%), 45.7% of them intravenously. The most prevalent genotype was G1a (66.2%), followed by G4 (11.3%). Ten of 90 patients evaluated for spontaneous cure (11%) cured the infection spontaneously, and 119 had treatment after a median time of 1.8 (0.7–4.6) months: sustained virological response (SVR) was achieved in 90.7% in the ITT and 94.7% in the PP analysis, with no differences regarding the direct-acting antiviral agents (DAA) combination used.

Conclusions: MSM infected by HIV with a RAHC were exposed to high-risk sexual behavior. Spontaneous
cure rate was low, while SVR after treatment was achieved by more than 90%.

Keywords

HCV HIV, MSM, Recently acquired hepatitis C

Introduction

The World Health Organization (WHO) has an ambitious pro-gram to eliminate viral hepatitis as a major public health threat by 2030. Specifically, a 90% reduction in new hepatitis C virus (HCV) infections and a 65% reduction of HCV-related deaths should be achieved by 2030.1 Due to the efficacy and tolerability of direct-acting antiviral agents (DAA), this plan should be possible; however, significant challenges as access to affordable diagnosis and treatment programs (mainly in low and middle-income coun-tries) are required to afford this plan.2

Another challenge for HCV elimination is the epidemic of HCV infections and reinfections described within the last two decades in men who have sex with men (MSM) in multiple metropolitan areas throughout the world.3–6 To address this problem, some recent guidelines recommend early treatment of recently acquired HCV (RAHC), especially in a population at higher risk of transmission.7–9 On the one hand, recent data from modeling studies and population cohorts suggest that an immediate treatment after HCV diagno-sis may be a cost-effective strategy when including prevention benefits.10,11 On the other hand, although data are still scarce, the rates of response to RAHC treatment with DAA show very high cure rates.12–14

The objectives of our study were, first, to describe sociodemo-graphic characteristics of PLHIV with RAHC in the Madrid area; second, to determine spontaneous cure in patients who did not start treatment very early; and third rates of sustained virological response (SVR) in patients who started treatment with DAA.

Methods

Ours was a multicenter, ambispective, observational study con-ducted in the city of Madrid (Spain). Eligible patients were MSM or transexual women, 18 years of age or older who had a documented HIV infection and a RAHC diagnosed since January 2017 to Decem-ber 2020. RAHC was defined according to the European Treatment Network for HIV, Hepatitis and Global Infectious Diseases (NEAT-ID) Consensus Panel definition of recently acquired hepatitis C virus infection.9 This is, having a positive anti-HCV IgG and a documented negative anti-HCV IgG in the previous 12 months or a positive HCV-RNA with a documented negative HCV-RNA or negative anti-HCV IgG in the last 12 months.

Eight centers in the public health system of the Madrid area par-ticipated in the study. The study had two phases. From January 1, 2019, to December 31, 2020, RAHC patients were invited to par-ticipate and prospectively enrolled the study. Patients diagnosed with RAHC between January 1, 2017, and December 31, 2018, were retrospectively reviewed.

Sociodemographic characteristics (age, race, place of birth), HIV-related variables (years since diagnosis, stage of infection, CD4 T cell lymphocytes count, and HIV viral load), and a history of sexu-ally transmitted diseases (STD) were recorded in the entire sample. In addition, prospectively included participants completed a self-reported survey that included questions about sexual behaviors (number of sexual partners, condom use, receptive anal sex, fist-ing practices), general drug use, and the use of chemsex related drugs within the last six months. The use of chemsex related drugs was considered when participants used mephedrone or other cathinones, crystal methamphetamine, or y-hydroxybutyrate (GHB)/y-butyrolactone (GBL). They also completed the Spanish ver-sion of the Hospital Anxiety and Depression scale (HADS) to assess anxiety and depression symptoms and answer questions about the way they thought they became infected with HCV.15

Concerning hepatitis C characteristics, HCV-RNA viral load and HCV genotype, were recorded. In the prospective phase of the study, a sample was collected and saved for subsequent phylogenetic analysis.

Evolution

A spontaneous cure was evaluated in patients who had at least two HCV-viral load measurements separated by at least one month.

When there was not a decrease of at least 2 log of HIV-RNA during the first month or undetectable HCV-RNA at month 6 spontaneous clearance was excluded. Patients who started treatment as soon as the diagnosis was performed were excluded from this analysis as spontaneous HCV clearance could not be excluded.

In patients treated with DAA, the time from diagnosis to treat-ment and type of DAA combination used were recorded.

Sustained viral response (SVR) was defined as an undetectable HCV RNA, 12 weeks after treatment. Results were given as inten-tion to treat (ITT) analysis and as per-protocol (PP) analysis, where missing patients were excluded.

Statistical analysis

Categorical variables were expressed as absolute and relative frequencies; continuous variables were expressed as median and interquartile ranges (IQR). Baseline characteristics between ret-rospective and prospective patients included in the study were compared using the Chi-squared or Fisher exact test for categor-ical variables and the T-test for continuous variables. A comparison of SVR regarding the DAA used was performed using the 32 test.

Results

Baseline characteristics

133 patients of 8 different centers were included in the study: 34 in 2017, 32 in 2018, 39 in 2019, and 28 in 2020.

Baseline characteristics are shown in Table 1. Median age (IQR) and median time since HIV diagnosis were 40 (34.3–46.1) and 8 (4–12) years, respectively. Overall, more than 90% of the patients had at least one STD, and 33.6% had previously hepatitis C. The most prevalent HCV genotype was G1a in 66.2% of the cases, followed by G4 (11.3%). The median baseline HCV viral load was 5.8 log10 IU/ml. Comparison between prospective and retrospective cohorts in sociodemographic and clinical characteristics are shown in Table 1. There were no statistically significant differences in any baseline characteristics except for age: patients included in the prospective cohort were older.

Regarding self-reported data completed by patients prospec-tively included (n = 67), 61 participants completed valid drug-related questions. Of them, 57.3% (n = 35) reported the use of chemsex related drugs in the last 6 months: cathinones (54.1%), GHB (47.6%), cocaine (27.9%), methamphetamine (26.2%), ketamine (6.4%) and ectasis (1.5%). None of the patients reported having used heroin. In the last six months, sixteen patients (26.2%) had used drugs intravenously and 6 (9.8%) anally.

Furthermore, 47 patients answer valid questions about sexual risk behaviors. Of them, 45 (91.8%) had unprotected anal sex, 26 (54.2%) had had more than ten sexual partners, and 13 (27.7%) had practiced fisting in the last six months. Forty-five patients answered a question about possible modes of having acquired HCV infection: 37 (82.2%) thought they could have acquired it by sexual rela-tionship, 5 (11.1%) by sharing needles or other injection drug use material, 9 (7.1%) by sharing sex toys or similar objects and 11 (8.7%) by sharing material while snorting drugs.

Finally, 46 participants completed valid HADS for screen anxiety and depression. Of them, 22 (47.8%) had scores suggestive of clinical mood disorders (depression sub-scale scores >8) and 16 (34.8%) suggestive of possible clinical anxiety (anxiety sub-scale scores >8).

Table 1. Characteristics of HIV infected MSM with recently acquired hepatitis C in Madrid.

Year	**Retrospective cohort 2017–2018 *n* = 66**	**Prospective cohort 2019–2020 *n* = 67**	**Total 133**	***p***
Age (years)	38.5 (33.2–44)	42.4 (36.2–48)	40 (34.3–46.1)	**0.03**
Origin				
Spanish	36 (59%)	46 (69.7%)	82 (64.6%)	**0.3**
Latin-American	24 (39.3%)	20 (30.3%)	44 (34.6%)	
Other	1 (1.6%)		1 (0.8%)	
Time of HIV infection (years)	8 (4.2–11)	7 (4–12)	8 (4–12)	**0.8**
On ART	63 (96.9%)	63 (95.5%)	126 (96.2%)	**0.6**
Previous STD	59 (90.8%)	61 (91%)	120 (90.9%)	**0.9**
STD one year before RAHC	17 (56.7%)	12 (41.4%)	58 (51.9%)	**0.6**
Previous HCV infection	21 (33.9%)	22 (33.3%)	43 (33.6%)	**0.9**
Use of chemsex associated drugs*	NR	35 (52.2)	35 (52.2)	**0.7**
More than 10 sexual partners in	NR	26 (54.2%)	26 (54.2%)	
the last 6 months				
HCV viral load (log IU/ml)	5.8 (4.8–6.2)	5.7 (4.7–6.5)	5.8 (4.8–6.4)	**0.4**
HCV genotype				
G1a	49 (74.2%)	39 (58.2%)	88 (66.2%)	**0.2**
G4	10 (15.1%)	5 (7.5%)	15 (11.3%)	
Other	2 (3%)	3 (4.5%)	5 (3.7%)	
Unknown	**5 (7.5%)**	**20 (29.8%)**	**25 (18.8%)**	

ART: antiretroviral drugs; STD: sexually transmitted diseases; RAHC: recently acquired hepatitis C.
* Mephedrone or other cathinone, methamphetamine, or GHB/GLB.

RAHC evolution

Only 90 patients could be evaluated for spontaneous cure (those who had at least two HCV-viral load measurements separated by at least one month before starting HCV treatment). Ten of them

spontaneously cleared HCV: 11% (95% CI 0.6–20). Among the other 123 patients (90 without spontaneous cure and 43 with early treat-ment), 119 started treatment, and 4 were lost of follow-up before HCV treatment.

Treatment was started at a median time of 1.8 months (0.7–4.6) since the diagnosis. DAA used was Elbasvir/Gazoprevir in 10 patients, Sofosbuvir/Ledipasvir in 29, Glecapre-bir/Pibrentasvir in 46, Sofosbuvir/Velpatasvir in 31 and Sofosbuvir/Velpatasvir/Voxilaprevir in 3.

SVR was 90.7% (108/119) in the ITT analysis and 94.7% (108/114) in the PP analysis. Six patients had HCV relapse 12 weeks after completing treatment. All relapses were with the same genotype. Reinfection could not be ruled out in four of them, as patients rec-ognized having recent high-risk sexual practices or the diagnosis coincided with another STD. Finally, 5 patients were lost to follow-up. There were no statistical differences in SVR regarding the DAA combination used (p = 0.7) [Fig. 1].

There were no significant differences in SVR regarding HCV genotype in the ITT analysis. SVR in the most prevalent genotypes were: 89.7% (70/78) in G1a and 100% (12/12) in G4 (p = 0.7). Only two patients were G3 infected, and both were treated with SOF/VEL. One of them achieved SVR, and the other was lost to follow-up. Baseline HCV viral load was neither associated with SVR: β 0.76 (0.54–1.56) for every log HCV increase (p = 0.9).

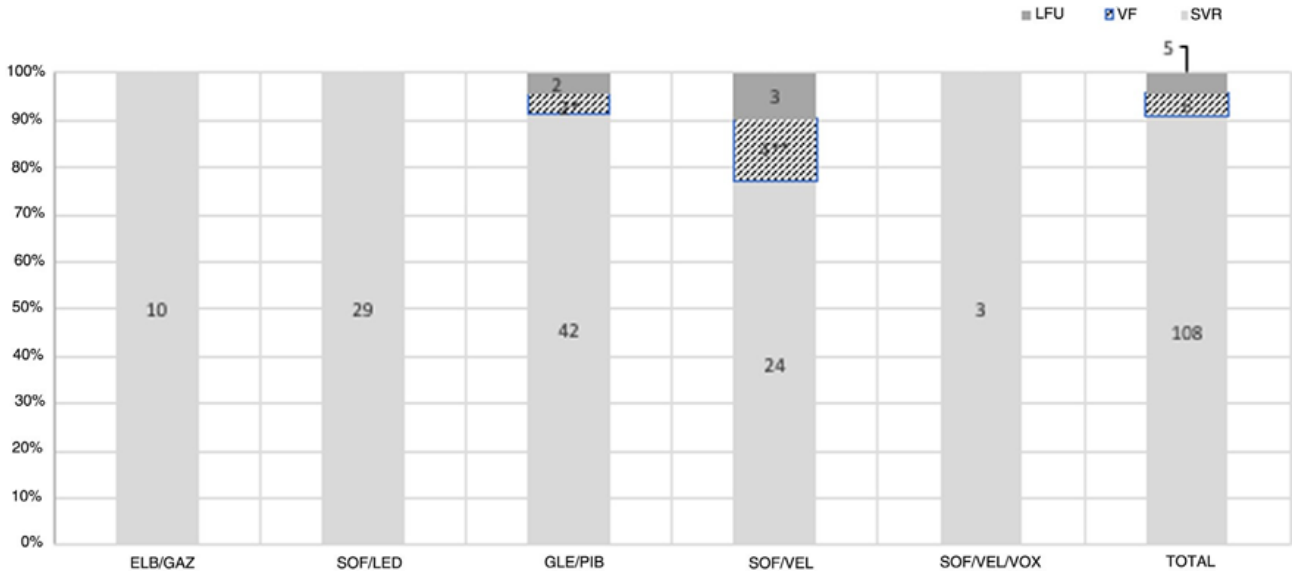

Fig. 1. Treatment response in recent hepatitis C infected PLHIV. PLHIV: people living with HIV; SVR: sustained virologic response; VF: virologic failure; LFU: lost to follow-up; ELB/GAZ: Elbasvir/Grazoprevir; SOF/LED: Sofosbuvir/Ledipasvir; GLE/PIB: Glecaprebir/Pibrentasvir; SOF/VEL: Sofosbuvir/Velpatasvir; SOF/VEL/VOX: Sofosbu-vir/Velpatasvir/Voxilaprevir. *Possible reinfection; **two possible reinfections, 1 bad adherence; ***no statistical differences were seen between different treatment used.

Discussion

Declines in HCV incidence and prevalence in MSM living with HIV have been reported in some countries such as Australia16 and Germany since the broad implementation of HCV treatment programs. Although Spain is one of the countries with the highest rates of HCV treatment and elimination,17 especially among PLHIV18 we did not observe this decrease in RAHC. Since 2016 Spain has had universal and unrestricted treatment for hepatitis C, which allowed us to carry out this study to assess the impact of treatment on high-risk people in the next years.

Absolute numbers of RAHC infections did not decrease during the last four years in 8 HIV reference centers in Madrid and were usually accompanied by risky sexual practices and other STIs. In 2020, we observe a slight decrease in the cases, although this is likely due to the lack of clinic visits due to the COVID-19 pandemic. Due to confinement policies in 2020, a greater decrease in cases should be expected. We believe multiple reasons can explain the lack of decrease cases observed in our population. First, as pre-viously reported, RAHC appeared in MSM-PLHIV with high-risk sexual behaviors.20,21 The acquisition of hepatitis C has been associated with risky sexual practices such as condomless anal sex, fisting, or having a high number of casual sexual partners co-existence of other STDs and other risky practices such as recreational drug use during sex (including intravenous drug use). As in previous stud-ies, our entire sample had high rates of having had at least another STD in their lifetime and the previous year to HCV diagnosis (90 and 52%, respectively). Moreover, the data collected in our group of patients prospectively included show high rates of condomless (92%), fisting practice (28%), a high number of casual sexual partners (54%), and use of chemsex related drug use (57%). Interestingly, most patients thought they had been infected by HCV during sex-ual relationships, but nearly 10% associated it with sharing needles, snorting paraphernalia, or sexual toys. These data highlight the need for multidisciplinary sexual health programs and a holistic approach to address this problem. Second, a hidden undiagnosed HCV population may be acting as a reservoir. In this context, some HIV-negative MSM have similar sexual risk practices and risk of HCV acquisition, but unlike HIV-infected MSM, STD screening is less frequent as they do not always routinely engage with the health care system.19,20

HCV re-infection either after spontaneous clearance or treatment-induced sustained viral response is a well-recognized phenomenon, especially in HIV-positive MSM with ongoing risk behaviors. In our sample, 43 (33.6%) patients from the retro-spective and prospective cohorts had an HCV reinfection. Similar data have also been reported in the German GECCO cohort6 and the Madrid-Core21 (reinfection rates of 5.93 patients-years among MSM HIV infected). In Madrid-Core, reinfections have been detected a median of 15 weeks after SVR, suggesting that patients continued to engage in risk behaviors shortly after or even during DAA therapy. Identifying new HCV infections should be based on whether the individual engages in risky activities associated with HCV transmission. However, the high rate of HCV reinfection in MSM underlines the difficulties in changing or modifying ongoing risk behavior. Fortunately, early HCV treatment as prevention has been followed by a dramatic decrease in new HCV infections in recent study reports from different countries in Europe.11,22

Since we did not have paired pre-and post-treatment samples, we could not classify rebound of viral load as relapse or reinfec-tion. A phylogenetic study was not carried out in six patients who relapsed with the same genotype. In fact, in 4 of the 6 patients, the diagnosis of reinfection was the most likely as they recognized high-risk sexual practices or RAHC diagnosis was concurrent with other STDs.

Over the last decade, the advent of efficacious and well-tolerated oral DAA treatments dramatically altered the treatment paradigm in chronic hepatitis C, increasing cure rates to more than 95%.7 Guidelines for chronic HCV infection generally recommend using pan-genotypic regimens wherever possible because of their very high efficacy and the ability to avoid genotyping. Data on the two pan-genotypic regimens of Sofosbuvir/Velpatasvir and Glecaprevir/Pibrentasvir in the

setting of recent infection are currently limited. A total of 108 patients with RAHC received antiviral treat-ment in a median time of less than two months from diagnosis. This is facilitated by universal access to therapy in our region and clini-cians' awareness of the need for early treatment in high-risk groups. Efficacy by intention-to-treat was very high (SVR >90%) and com-parable to other studies in people with HIV. No differences were observed between the different DAA used, suggesting that any reg-imen used for chronic hepatitis C is useful for RAHC. Although there are few data on treatment response to DAA for RAHC in clinical tri-als, they show high rates of SVR. For example, 8 weeks of SOF/LED obtained an SVR of 100% in 27 PWHIV12 and 8 weeks of ELB/GAZ obtained an SVR of 99% in 80 patients.23 According to these data and ours, an Austrian clinical setting study showed 100% of SVR in 38 RAHC PLHIV, treated with different combinations following rec-ommendations for chronic hepatitis C treatment.24 Treatment was well-tolerated, and there were no treatment interruptions due to adverse events. On note, 3 patients received SOF/VEL/VOX although this regimen is indicated as second line after treatment failure. All three cases were reinfections and not relapses (negative HCV-RNA was observed 3 months after the end of the previous treatment) but their doctors decided to prescribe this treatment.

On the contrary, a spontaneous cure is low, 11% in our cohort, like other reports. Rates of spontaneous viral clearance in HIV-positive MSM with recently acquired hepatitis C in the large PROBE-C cohort have been low at 11.8%.25 This proves that follow-ing a recently acquired HCV infection, transition to chronic hepatitis C is the most common outcome in individuals with or without HIV infection. With the high rates of treatment SVR and the high rates of reinfection in this high-risk population, this data suggests that treatment deferral to await spontaneous clearance might not be justified. Treatment delays may lead to HCV transmission in the setting of ongoing risk behavior.

Our study has some limitations. First, to have a follow-up over the years, we had to include years 2017 and 2018 retrospectively. We acknowledge that data collection rigor is not the same. How-ever, all HCV infected patients who received treatment in Madrid have to be included in a compulsory prospective registry.25 For this reason, we do not believe we have missed any patients with RAHC, at least those who have received treatment. Second, due to the COVID-19 pandemic, patients had fewer clinical visits; therefore, the number of cases in 2020 may have been underestimated. How-ever, we believe that our data shows that RAHC in HIV-MSM with high-risk sexual behaviors continues to be an important handicap in terms of HCV elimination in developed countries. Our study also highlights the high rates of SVR in RAHC treated very early in a clinical setting.

In conclusion, we did not observe a decrease in RAHC cases among HIV-MSM with high-risk sexual practices since the imple-mentation DAA treatment. Spontaneous cure rates are low, while SVR after treatment is above 90%. Our results reinforce recent rec-ommendations of AASLD and EACS guidelines for initiating HCV treatment as soon as possible, without waiting for spontaneous resolution.

Declarations

Ethics approval and consent to participate

The study was approved by La Paz Hospital Ethics committee. All patients were informed before any study procedure was performed and signed informed consent. Study data were all anonymized and collected using the tool Research Electronic Data Capture (REDCap) hosted at "Association Ideas for Health".26 All research was carried out following the right to privacy, as stipulated in the Organic Regu-lation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016, on data protection (GDPR), on the protection of personal data, and the Declaration of Helsinki.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Protocol design: LMC, AGB, SR, JHG, PR.
Patient selection, include data on base-data: LMC, AG, OB, JV, CR, MJV, JS, BA, MP, IS, PR.
Statistical analysis: LMC, PR.
Sample processing: SR, DSC.
Manuscript writing: LMC, AGB, PR.
Manuscript review: All
English review: JCS

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Appendix 1

Centers involved in Long Term Non-Progressors (LTNPs) cohort

Centro Sandoval - Madrid
Hospital 12 de Octubre - Madrid
Hospital Arnau de Vilanova - Lleida
Hospital Asturias
Hospital Bellvitge - Barcelona
Hospital Castellón
Hospital Clínic - Barcelona
Hospital Donostia - San Sebastián
Hospital Elche - Alicante
Hospital Germans Trias i Pujol - Badalona
Hospital Gregorio Marañón - Madrid
Hospital Joan XXIII - Tarragona
Hospital La Fe - Valencia
Hospital La Paz/Carlos III - Madrid
Hospital La Princesa - Madrid
Hospital Navarra - Pamplona
Hospital Parc Taulí- Sabadell
Hospital Ramón y Cajal - Madrid
Hospital San Cecilio - Granada
Hospital San Pedro - Logroño
Hospital Son Dureta - Mallorca
Hospital Virgen del Rocío – Sevilla

Supplementary Materials

Supplementary Table 1. STrengthening the REporting of Genetic Association studies (STREGA) reporting recommendations, extended from STROBE Statement

Item	Item no	STROBE Guideline	Extension for Genetic Association Studies (STREGA)	Page no
Title and Abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract.		1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found.		3
Introduction				
Background rationale	2	Explain the scientific background and rationale for the investigation being reported.		4-5
Objectives	3	State specific objectives, including any pre-specified hypotheses	***State if the study is the first report of a genetic association, a replication effort, or both.***	5
Methods				
Study design	4	Present key elements of study design early in the paper.		6
Setting	5	Describe the setting, locations and relevant dates, including periods of recruitment, exposure, follow-up and data collection.		6
Participants	6	(a) **Cohort study –** Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. **Case–control study –** Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. **Cross-sectional study –** Give the eligibility criteria, and the sources and methods of selection of participants.	***Give information on the criteria and methods for selection of subsets of participants from a larger study, when relevant.***	6
		(b) Cohort study – For matched studies, give matching criteria and number of exposed and unexposed. **Case–control study –** For matched studies, give matching criteria and the number of controls per case.		
Variables	7	(a) Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	***(b) Clearly define genetic exposures (genetic variants) using a widely –used nomenclature system. Identify variables likely to be associated with population stratification (confounding by ethnic origin).***	6
Data sources measurement	8*	(a) For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.	***(b) Describe laboratory methods, including source and storage of DNA, genotyping methods and platforms (including the allele calling algorithm used, and its version), error rates and call rates. State the laboratory /centre where genotyping was done. Describe comparability of laboratory methods if there is more than one group. Specify whether genotypes were assigned using all of the data from the***	6-7

			study simultaneously or in smaller batches.	
Bias	9	(a) Describe any efforts to address potential sources of bias.	***(b) For quantitative outcome variables, specify if any investigation of potential bias resulting from pharmacotherapy was undertaken. If relevant, describe the nature and magnitude of the potential bias, and explain what approach was used to deal with this.***	7
Study size	10	Explain how the study size was arrived at.		6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why.	***If applicable, describe how effects of treatment were dealt with.***	6-7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding.	***State software version used and options (or settings) chosen.***	7
		(b) Describe any methods used to examine subgroups and interactions.		7
		(c) Explain how missing data were addressed.		
		(d) **Cohort study –** If applicable, explain how loss to follow-up was addressed. **Case–control study –** If applicable, explain how matching of cases and controls was addressed. **Cross-sectional study –** If applicable, describe analytical methods taking account of sampling strategy.		
		(e) Describe any sensitivity analyses.		
			(f) State whether Hardy-Weinberg equilibrium was considered and, if so, how.	7
			(g) Describe any methods used for inferring genotypes or haplotypes.	7
			(h) Describe any methods used to assess or address population stratification.	7
			(i) Describe any methods used to address multiple comparisons or to control risk of false positive findings.	7
			(j) Describe any methods used to address and correct for relatedness among subjects.	7
Results				
Participants	13*	(a) Report the numbers of individuals at each stage of the study – e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up and analysed.	***Report numbers of individuals in whom genotyping was attempted and numbers of individuals in whom genotyping was successful.***	8
		(b) Give reasons for non-participation at each stage.		
		(c) Consider use of a flow diagram.		
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders.	***Consider giving information by genotype.***	8
		(b) Indicate the number of participants with missing data		

		for each variable of interest.		
		(c) **Cohort study –** Summarize follow-up time, e.g. average and total amount.		
Outcome data	15*	**Cohort study –** Report numbers of outcome events or summary measures over time.	***Report outcomes (phenotypes) for each genotype category over time***	8
		Case–control study – Report numbers in each exposure category, or summary measures of exposure.	***Report numbers in each genotype category***	
		Cross-sectional study – Report numbers of outcome events or summary measures.	***Report outcomes (phenotypes) for each genotype category***	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence intervals). Make clear which confounders were adjusted for and why they were included.		8
		(b) Report category boundaries when continuous variables were categorized.		
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.		
			(d) Report results of any adjustments for multiple comparisons.	
Other analyses	17	(a) Report other analyses done – e.g. analyses of subgroups and interactions, and sensitivity analyses.		8
			(b) If numerous genetic exposures (genetic variants) were examined, summarize results from all analyses undertaken.	
			(c) If detailed results are available elsewhere, state how they can be accessed.	
Discussion				
Key results	18	Summarize key results with reference to study objectives.		9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.		10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.		9-10
Generalizability	21	Discuss the generalizability (external validity) of the study results.		9-10
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.		12

STROBE: STtrengthening the Reporting of Observational Studies in Epidemiology

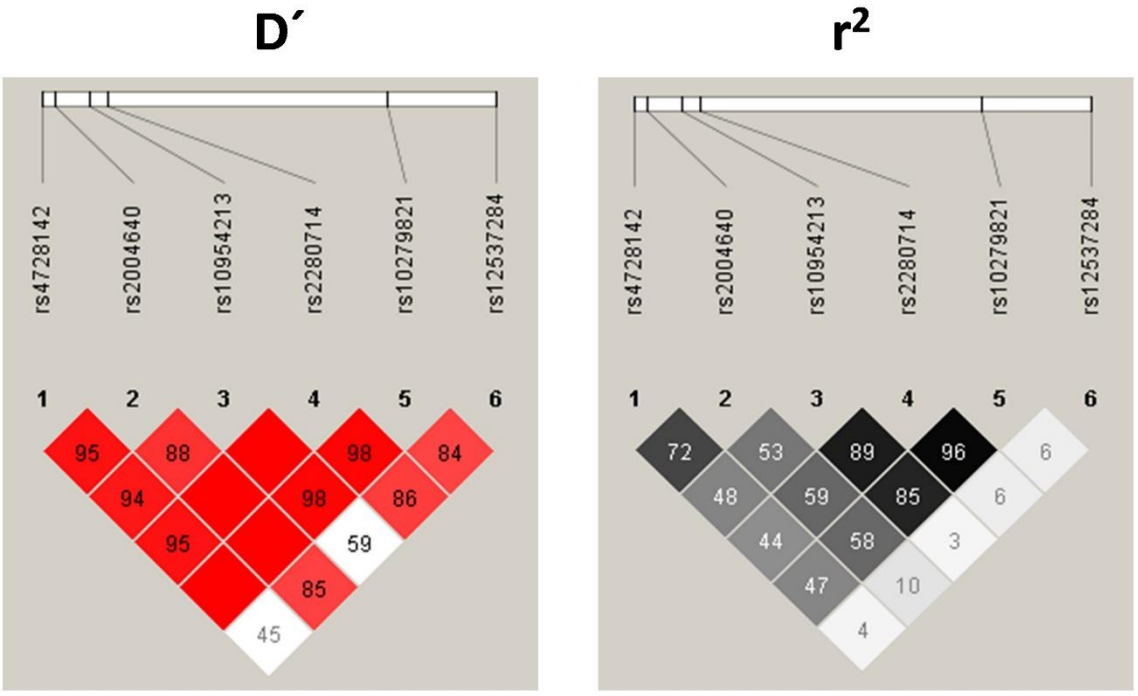
*Give information separately for cases and controls in case–control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Supplementary Table 2. Characteristics of *IRF5–TNPO3* polymorphisms in LTNPs and control group.

		Distribution of genotypes (1)			HWE (2)	
SNPs	**Genotype**	**Control group**	**LTNPs**	***p*-value**	**Control group**	**LTNPs**
rs4728142	n=293					
	GG	33 (30.0%)	55 (30.1%)	0.933	0.451	0.658
	AG	51 (46.4%)	88 (48.1%)			
	AA	26 (23.6%)	40 (21.9%)			
rs2004640	n=289					
	TT	36 (32.7%)	47 (26.3%)	0.495	0.563	1.000
	GT	51 (46.4%)	90 (50.3%)			
	GG	23 (20.9%)	42 (23.5%)			
rs10954213	n=293					
	AA	46 (41.8%)	67 (36.6%)	0.482	0.529	0.755
	AG	53 (48.2%)	90 (49.2%)			
	GG	11 (10.0%)	26 (14.2%)			
rs2280714	n=293					
	TT	52 (47.3%)	72 (39.3%)	0.357	0.659	0.425
	CT	49 (44.5%)	90 (49.2%)			
	CC	9 (8.2%)	21 (11.5%)			
rs10279821	n=293					
	CC	52 (47.3%)	71 (38.8%)	0.316	0.498	0.198
	CT	50 (45.5%)	93 (50.8%)			
	TT	8 (7.3%)	19 (10.4%)			
rs12537284	n=292					
	GG	81 (74.3%)	136 (74.3%)	0.951	0.447	0.758
	AG	25 (22.9%)	43 (23.5%)			
	AA	3 (2.8%)	4 (2.2%)			

Statistic: (1), Differences in the genotype's distribution between HIV patients and controls; (2), Hardy-Weinberg equilibrium. P-values were calculated by chi-squared. P-values were calculated by chi-squared. **Abbreviations**: HIV: human immunodeficiency virus; HWE: Hardy-Weinberg equilibrium; IRF5: interferon regulatory factor 5; LTNP: long-term nonprogressor; SNP: single nucleotide polymorphism; TNPO3: transportin 3.

Supplementary Figure 1. Pairwise linkage disequilibrium (LD) pattern for *IRF5–TNPO3* polymorphisms. The intensity of red or grey decreases with decreasing D´ and r2 values. The genomic location of SNPs is indicated on top. The diagonal represents an SNP, and the square represents a pairwise comparison between two SNPs, indicating the magnitude of LD (D´ and r^2). D´ and r^2 vary from 0 (absence) to 100 (complete). **Abbreviations**: D´: D-prime or proportion of the possible LD that was present between two SNPs; HIV: human immunodeficiency virus; IRF5: interferon regulatory factor 5; LD: linkage disequilibrium; r^2: square of the correlation coefficient; SNP: single nucleotide polymorphism; TNPO3: transportin 3.



Supplementary Table 3. Genetic association of *IRF5–TNPO3* polymorphisms with HIV elite control.

SNPs	Inheritance	Genotypes	OR (95%CI)	p-value	aOR (95%CI)	p-value
rs4728142	Dominant	GG vs. AG/AA	0.98 (0.52 - 1.85)	0.961	0.99 (0.52 - 1.88)	0.963
rs4728142	Recessive	GG/AG vs. AA	1.72 (0.85 - 3.49)	0.134	1.80 (0.87 - 3.70)	0.112
rs4728142	Additive	nA	1.19 (0.79 - 1.79)	0.403	1.21 (0.80 - 1.83)	0.373
rs2004640	Dominant	TT vs. GT/GG	0.50 (0.25 - 0.98)	**0.045**	0.49 (0.25 - 0.97)	**0.041**
rs2004640	Recessive	TT/GT vs. GG	0.71 (0.35 - 1.43)	0.339	0.76 (0.37 - 1.55)	0.452
rs2004640	Additive	nG	0.67 (0.44 - 1.03)	0.068	0.68 (0.45 - 1.05)	0.084
rs10954213	Dominant	AA vs. AG/GG	0.54 (0.29 - 0.99)	**0.046**	0.51 (0.28 - 0.95)	**0.035**
rs10954213	Recessive	AA/AG vs. GG	0.80 (0.35 - 1.86)	0.606	0.74 (0.32 - 1.75)	0.495
rs10954213	Additive	nG	0.69 (0.44 - 1.06)	0.092	0.66 (0.42 - 1.03)	0.064
rs2280714	Dominant	TT vs. CT/CC	0.52 (0.28 - 0.94)	**0.031**	0.50 (0.27 - 0.91)	**0.024**
rs2280714	Recessive	TT/CT vs. CC	0.66 (0.26 - 1.69)	0.388	0.65 (0.25 - 1.67)	0.371
rs2280714	Additive	nC	0.63 (0.40 - 0.99)	**0.043**	0.61 (0.38 - 0.97)	**0.036**
rs10279821	Dominant	CC vs. CT/TT	0.49 (0.27 - 0.90)	**0.021**	0.47 (0.26 - 0.87)	**0.017**
rs10279821	Recessive	CC/CT vs. TT	0.80 (0.31 - 2.10)	0.652	0.79 (0.30 - 2.09)	0.632
rs10279821	Additive	nT	0.63 (0.39 – 0.99)	**0.05**	0.61 (0.38 - 0.98)	**0.041**
rs12537284	Dominant	GG vs. AG/AA	0.99 (0.51 - 1.92)	0.976	1.01 (0.51 - 1.97)	0.988
rs12537284	Recessive	GG/AG vs. AA	0.37 (0.04 - 3.61)	0.391	0.35 (0.04 - 3.51)	0.372
rs12537284	Additive	nA	0.92 (0.51 - 1.65)	0.772	0.92 (0.51 - 1.68)	0.793

Statistics: Data were calculated by binary logistic regression adjusted by gender, age at HIV diagnosis, and injecting drug use (IDU) as the risk factor for HIV acquisition. Significant differences are shown in bold. **Abbreviations**: 95%CI: 95% confidence interval; OR: odds ratio; aOR: adjusted odds ratio; HIV: human immunodeficiency virus; IRF5: interferon regulatory factor 5; LTNP: long-term non-progressors; LTNP-EC: long-term non-progressors who are elite controllers; LTNP-non-EC: long-term non-progressors who are not elite controllers; TNPO3: transportin 3.