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Comment on “Characteristics of B-Cell Lymphomas in HIV/HCV-Coinfected Patients During the Combined Antiretroviral Therapy Era: An ANRS CO16 LYMPHOVIR Cohort Study”

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To the Editors

In their recent manuscript studying on French National Agency for Research on AIDS and Viral Hepatitis ANRS-CO16 Lymphovir cohort, Terrier *et al.* observed a high proportion of a distinct B-cell non-Hodgkin lymphoma (NHL) subtype in HIV/HCV-coinfected patients, when compared to HIV-monoinfected patients, in the era of combined antiretroviral therapy (cART): 5 of 6 (83%) coinfecting patients versus 1 of 33 (3%) monoinfected patients presented with marginal zone/lymphoplasmacytic lymphoma (MZL/LPL).¹ These coinfecting patients were more frequently intravenous drug users and had a tendency toward higher CD4⁺ T lymphocyte counts than HIV-monoinfected NHL patients. Patients in both groups showed comparable plasma HIV RNA concentrations. The authors described the

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Conflicts of Interest

All authors declare that they have no potential conflicts of interest.

clinical and epidemiological characteristics of HIV/HCV-coinfected NHL patients and concluded that chronic antigenic stimulation by HCV may contribute to lymphomagenesis among HIV-infected patients, resulting in the development of lymphomas of the MZL/LPL subtype. This is a striking observation, and led us to explore this hypothesis in the Multicenter AIDS Cohort Study (MACS).

The Multicenter AIDS Cohort Study (MACS), established in 1983, enrolled 6,972 men who have sex with men (MSM) from four metropolitan areas between 1984 and 2003.^{2–5} NHL is ascertained through self-report with confirmation by pathology records and state cancer registries, or is identified at autopsy. NHL subtypes are also defined through review of pathology reports. HCV status is determined by testing both antibodies to HCV (anti-HCV) using enzyme immunoassay (ADVIA Centaur HCV assay), and serum HCV RNA levels by PCR (COBAS AmpliPrep TaqMan HCV Assay). Anti-HCV and HCV RNA testing was performed at multiple time points retrospectively on stored serum from the baseline study visit through 2001, and prospectively every six months since 2001. Only 38 (0.6%) MACS participants had either no HCV test at all ($n = 19$) or inconclusive status at their enrollment visit ($n = 19$).

For this analysis, we examined 190 HIV-infected MACS participants diagnosed with NHL by July 2010, as described in previous studies.^{6, 7} HCV testing was done within one year of the baseline study visit in 184 of these 190 cases (97%), and 189 (99%) had at least one follow-up HCV test after baseline. The average time from baseline study visit to NHL diagnosis was 7.6 years (median: 7.3, interquartile range [IQR]: 4.8–10.1 years). A participant was considered HCV-negative if all available HCV antibody tests prior to NHL diagnosis date were negative. A participant was considered to have cleared his HCV infection if he had a negative HCV RNA test result prior to NHL diagnosis date preceded by either (1) at least two positive anti-HCV test results, (2) at least two results of detectable HCV RNA, or (3) a detectable HCV RNA level at study baseline. A participant was considered chronically HCV-infected if he had a positive HCV RNA test result at the time of NHL diagnosis preceded by either a positive anti-HCV or HCV RNA result. Of the 190 NHL cases, 164 were HCV-negative (HIV-monoinfected), 18 were chronically HCV-infected, and 7 had cleared HCV infection.

Table 1 shows distributions of selected characteristics for NHL cases by HCV status. Most NHL cases were diagnosed in the pre-cART era, and only 14 of them, all HIV-monoinfected, received cART, with a median of 2.8 (IQR: 1.3–4.9) years from cART initiation to NHL diagnosis. All case groups had a similar distribution of HIV RNA levels at the time of NHL diagnosis ($P=0.910$). Among HIV/HCV-coinfected cases, more than half had their first positive results of anti-HCV and/or HCV RNA level at least 5 years prior to lymphoma diagnosis (71% and 56% of cases with cleared HCV and chronic HCV infection, respectively). A higher percentage of HIV/HCV-coinfected cases who cleared their HCV infection (71%) had NHL of the central nervous system compared to the other case groups (71% versus 29% and 22%, $P=0.056$). Among cases of systemic NHL, we did not observe a difference in subtype distributions across case groups ($P=0.679$), although sample size limits statistical power. No cases with coinfection were diagnosed with MZL/LPL. Two HIV-

monoinfected cases, who never received cART, were diagnosed with lymphoplasmacytic lymphoma.

In contrast to the Terrier *et al.* manuscript, there were no cases of MZL/LPL among HIV/HCV-coinfected patients in the MACS. Therefore, their suggestion that lymphomagenesis results from chronic HCV antigenic stimulation requires further study for confirmation. Further work to assess the association between HCV and specific B-cell NHL subtypes in HIV-infected populations is warranted.

There are several important differences between participants in the MACS and the French ANRS-CO16 Lymphovir cohort that should also be noted. The MACS is a population of MSM, and the NHL diagnoses were identified mainly in the pre-cART era. Only 14 participants with NHL had received cART; 7/14 (50%) of these cases had diffuse large B-cell lymphoma. One important limitation of the MACS data is a lack of tumor samples to verify subtypes via immunohistochemistry staining for all cases, as was done in the Terrier *et al.* paper.

cART was introduced 18 years ago, yet surprisingly only one-third of people living with HIV in the U.S. are receiving treatment.⁸ While there is an ongoing HCV outbreak among HIV-infected MSM,^{9, 10} very few studies have examined HCV status in patients with NHL in this population. Inspired by the recent work of Terrier *et al.*, we presented NHL subtypes of mostly cART naïve patients by HCV status in a MSM cohort.

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Table 1

Select characteristics of 189 HIV-infected non-Hodgkin lymphoma (NHL) patients in the Multicenter AIDS Cohort Study according to HCV infection status at NHL diagnosis date

	HIV monoinfected (n=164)	HIV/HCV coinfectd (n=25)		p ²
		Cleared HCV (n=7)	Chronic HCV (n=18)	
Age (years) at diagnosis, n (%)				
Median (IQR)	41 (36, 46)	37 (37, 39)	45 (43, 48)	
21–30	13 (8)	0	0	
31–40	62 (38)	6 (86)	2 (11)	
41–50	62 (38)	0	13 (72)	
> 50	28 (17)	1 (14)	3 (17)	0.006
CD4 ⁺ T-cell count (cells/mm ³) at diagnosis, n (%)				
Median (IQR)	82.5 (23, 310)	87 (23, 392)	83 (69, 196)	
< 100	85 (51)	4 (57)	11 (61)	
100–300	37 (23)	1 (14)	4 (22)	
> 300	42 (26)	2 (29)	3 (17)	0.930
Years of HIV infection prior to diagnosis ³ , n (%)				
Median (IQR)	6.9 (4.6, 9.3)	6.1 (5.0, 7.3)	6.7 (4.5, 9.5)	
< 5 years	52 (31)	2 (29)	5 (28)	
5–10 years	78 (47)	5 (71)	11 (61)	
> 10 years	35 (21)	0	2 (11)	0.551
cART exposure, n (%)				
< 12 months prior to NHL diagnosis	2 (1)	0	0	
12 months prior to NHL diagnosis	12 (7)	0	0	0.817
HIV RNA (log ₁₀) at NHL diagnosis, n (%)				
Median (IQR)	5.2 (4.8, 5.6)	5.3 (5.0, 5.7)	5.1 (4.3, 5.4)	
Non-detectable	3 (2)	0	0	
< 4	28 (17)	1 (14)	4 (22)	
4–5	46 (28)	1 (14)	4 (22)	
5–6	81 (49)	5 (71)	10 (56)	
> 6	10 (6)	0	0	0.910
Years between the first evidence for HCV infection and NHL diagnosis ⁴ , n (%)				
Median (IQR)	--	5.8 (2.8, 8.8)	6.2 (4.0, 9.1)	
< 1 year		0	2 (11)	
1–3 years	--	2 (29)	2 (11)	
3–5 years	--	0	4 (22)	
5–8 years	--	3 (42)	3 (17)	
> 8 years	--	2 (29)	7 (39)	0.374
Tumor subtype, N (%)				

	HIV monoinfected (n=164)	HIV/HCV coinfectd (n=25)		<i>p</i> ²
		Cleared HCV (n=7)	Chronic HCV (n=18)	
Systemic	116 (71)	2 (29)	14 (78)	
Diffuse large B cell	59	1	10	
Burkitt lymphoma (BL)/BL-like	18	0	1	
Marginal zone/lymphoplasmacytic lymphoma	2	0	0	
Diffuse mixed small and large cell lymphoma	1	0	0	
Follicular lymphoma (grade 3)	2	0	0	
Unknown/Not specified	34	1	3	0.679 ⁵
Central nervous system	48 (29)	5 (71)	4 (22)	0.056 ⁶
Tumor EBV status, n (%)				
Not tested	89 (54)	4 (57)	8 (44)	
Tested	75 (46)	3 (43)	10 (56)	
Negative	23 (31)	0	5 (50)	
Positive	52 (69)	3	5 (50)	0.205

IQR inter-quartile range; *ART* antiretroviral therapy; *cART* combined antiretroviral therapy;

¹ Cleared HCV infection: at least two positive anti-HCV and/or HCV RNA level followed by non-detectable HCV RNA level at NHL diagnosis date. Chronic HCV infection: at least one positive result of anti-HCV and/or HCV RNA preceding lymphoma with detectable HCV RNA levels at NHL diagnosis date. If a participant who had positive anti-HCV and never had HCV RNA test, his HCV status was incomplete.

² Fisher's exact test.

³ For HIV-prevalent cases at cohort entry, the year of HIV infection is date of baseline visit to NHL diagnosis date.

⁴ First positive result of anti-HCV and/or serum HCV RNA level.

⁵ Systemic lymphoma subtypes.

⁶ Distribution of systemic versus central nervous system lymphoma.