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Persistence of CXCR4-tropic virus in people living with four-class drug-resistant HIV and its clinical impact in the modern antiretroviral era

Rebecka Papaioannu Borjesson [1,2]*, Sara Diotallevi[2], Riccardo Lolatto[2], Giovanni Cenderello[3], Laura Comi[4], Antonio Cascio [5], Annalisa Saracino[6], Tommaso Clemente [1,2], Maria Mazzitelli[7], Sergio Lo Caputo[8], Daniele Armenia[9], Maria Mercedes Santoro[10], Antonella Castagna[1,2] and Vincenzo Spagnuolo [2] on behalf of PRESTIGIO Study Group†

[1]Infectious Diseases, Vita-Salute San Raffaele University, Milan, Italy; [2]Infectious Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy; [3]Infectious Disease Unit, Sanremo Hospital, Sanremo, Italy; [4]Infectious Disease, ASST Papa Giovanni XXIII, Bergamo, Italy; [5]Infectious and Tropical Diseases Unit—Department of Health Promotion, Maternal and Infant Care, Internal Medicine and Medical Specialties, University of Palermo, Palermo, Italy; [6]Clinic of Infectious Diseases, University of Bari, Bari, Italy; [7]Infectious Diseases Unit, Azienda Ospedale-Università Padova, Padova, Italy; [8]Clinic of Infectious Diseases, Department of Clinical and Surgical Sciences, University of Foggia, Foggia, Italy; [9]Departmental Faculty, Saint Camillus International University of Health Sciences, Roma, Italy; [10]Department of Experimental Medicine, University of Rome 'Tor Vergata', Roma, Italy

*Corresponding author. E-mail: papaioannu.rebecka@hsr.it
†Study Group team members are listed in the Acknowledgements section.

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Background: CXCR4-tropic HIV seems to be associated with more clinical events than CCR5-tropic virus.

Objectives: This study aims to describe the effect of the persistence of CXCR4-tropic virus on the occurrence of clinical events in people with four-class drug-resistant HIV.

Methods: This is a retrospective study on people with four-class drug-resistant HIV from the PRESTIGIO Registry, with at least two HIV-tropism determinations during follow-up. Follow-up accrued from the date of the first four-class drug resistance evidence (baseline) until death, loss to follow-up or freezing date (31 December 2023). Univariable Poisson regression was used to estimate and compare incidence rates of clinical events. Predictors of clinical events were assessed by multivariable Poisson regression.

Results: A total of 144 people with four-class drug-resistant HIV [47 (33%) with persistent CXCR4-tropism, 39 (27%) with persistent CCR5-tropism and 58 (40%) with a tropism switch during follow-up] were included with a median follow-up of 7.80 years (IQR = 5.80–10.6). Overall, 117 (81.3%) 4DR-PLWH experienced at least one clinical event during follow-up [incidence rate = 32.5 (95% CI = 29.3–35.9)]. The persistence of CXCR4-tropic virus was associated with an increased risk of HIV-related events among people living with four-class drug-resistant HIV, even in modern ART era. After adjusting for age, sex at birth and CD4+/CD8+ at baseline, standardized viremia copy-years [adjusted-incidence rate ratio = 1.66 (95% CI = 1.24–2.26), $P < 0.001$] and persistent CXCR4-tropism [adjusted-incidence rate ratio: 2.01 (95% CI = 1.04–3.91), $P = 0.037$] were associated with the occurrence of HIV-related events.

Conclusions: Our findings confirm CXCR4-tropism as a marker of HIV progression also in the four-class drug-resistant population, suggesting the need of further prioritization of viro-immunological control and studies of pathogenic mechanisms in presence of CXCR4-tropic multidrug-resistant viral strains.

Introduction

HIV requires a co-receptor to enter target cells in addition to CD4+ T-cells[1]; these cells can express the chemokine receptors cysteine-cysteine receptor 5 (CCR5) or cysteine-X-cysteine receptor 4 (CXCR4). Virus strains are classified according to their capacity to infect CD4+ T-cells using either or both of these co-receptors.[1]

CXCR4-tropic HIV virus seems to be associated with a greater decrease in CD4+ cell count and more clinical events than CCR5-tropic virus.[2]

It is now known that individuals with four-class drug-resistant HIV [4DR-PWH; resistant to nucleoside reverse transcriptase inhibitors (NRTIs), non-NRTIs (NNRTIs), protease inhibitors (PIs) and integrase strand transfer inhibitors (INSTIs)] are characterized by a high incidence of clinical events, both AIDS- and non-AIDS-related.[3]

To our knowledge, no studies have explored the correlation between HIV-tropism and the occurrence of clinical events in this fragile population.

The aim of our study was to describe the effect of the persistence of CXCR4-tropic virus on the occurrence of clinical events in 4DR-PWH.

Methods

This is a retrospective cohort study on 4DR-PWH from the PRESTIGIO Registry (NCT04098315), with at least two HIV-tropism determinations during follow-up.

PRESTIGIO is an Italian registry-based cohort of adults with HIV resistant to NRTIs, NNRTIs, PIs, and INSTIs, followed in 33 actively enrolling centres (protocol approved by the Ethics Committees of the participating centres).[4]

Follow-up accrued from the date of the first four-class drug resistance evidence (baseline) until death, loss to follow-up or freezing date (31 December 2023).

HIV-co-receptor tropism was determined by V3-loop Sanger sequencing, on HIV-DNA if viremia was suppressed and on HIV-RNA in PWH with detectable viremia, and we defined tropism as persistent if it remained unchanged during follow-up. HIV-1-tropism was inferred through the Geno2Pheno algorithm (https://coreceptor.geno2pheno.org/).

Individuals with sequences having false positive rate > 10% were considered infected with a CCR5-tropic virus.

We grouped individuals with persistent CCR5- and dual-mixed tropism, comparing them to those with persistent CXCR4-tropism to improve statistical power and interpretability, given the stronger association of CXCR4-tropism to advanced HIV disease and distinct immunopathogenic features.[2]

Clinical events were divided, according to the CDC 1993 classification,[5] into AIDS-defining events, HIV-related events, HIV-related infections (oral candidiasis, herpes zoster, tuberculosis, *Mycobacterium* infections, *Pneumocystis jirovecii* pneumonia, cryptococcosis, *Cytomegalovirus* infection) and non-HIV-related events (non-HIV-related infections, major adverse cardiovascular events, virus-related malignancies, non-virus-related malignancies).

Individuals' characteristics were described through median (IQR) or frequency (percentage) and compared using the χ^2, Fisher's exact test or the Mann–Whitney *U*-test, as appropriate.

Standardized viremia copy-years, based on the post-baseline viral load (VL) history of each individual, was calculated through the trapezoidal rule approximation[6] and adjusted for the individual time difference between the first and last VLs considered.

Univariable Poisson regression was used to estimate and compare incidence rates (IRs) and corresponding 95% CI of clinical events; IRs were calculated as the number of episodes per 100-person-years of follow-up (PYFU).

Predictors of clinical events were assessed by multivariable Poisson regression. Covariates considered clinically relevant were included in the model. Estimates of adjusted incidence rate ratios (IRRs) and 95% CIs were reported. Two-sided *P*-values of <0.05 were considered significant. Statistical analyses were performed with R (R Foundation for Statistical Computing, Vienna, Austria, release 4.2.3).

Results

A total of 144 4DR-PWH with at least two tropism determinations during follow-up were included, with a median time between tropism determinations of 5.3 years (IQR = 3.6–8.1). At baseline, 110 individuals (76.4%) were males, with a median age of 49.8 years (IQR = 44.2–53.6). The median time since HIV diagnosis was 21.3 years (IQR = 17.7–26.0), and the median duration of antiretroviral therapy (ART) was 18.2 years (IQR = 14.5–21.4). Over 142 4DR-PWH with at least two HIV-tropism and at least two VL determinations during follow-up, the median standardized viremia copy-years was 667 copies/mL (IQR = 86.2–6484).

Tropism determination at baseline and its changes during follow-up are reported in Table S1 (available as Supplementary data at *JAC* Online).

Baseline characteristics, according to HIV-co-receptor tropism, are reported in Table 1. No statistically significant differences were found in clinical and immunovirological characteristics between the two groups.

Among 144 4DR-PWH, 47 (33%) had a persistent CXCR4-tropism, 39 (27%) individuals had a persistent CCR5-tropism and 58 (40%) individuals experienced a tropism switch during follow-up.

During a median follow-up of 7.8 years (IQR = 5.8–10.6), 117 (81.3%) 4DR-PWH experienced a total of 381 clinical events [IR = 32.5 (95% CI = 29.3–35.9)/100-PYFU]. The most frequent clinical events were non-HIV-related infections [84 events among 47 4DR-PWH; IR = 7.16 (95% CI = 5.7–8.9)/100-PYFU], while the less frequent were virus-related malignancies [four events among four 4DR-PWH; IR = 0.34 (95% CI = 0.1–0.9)/100-PYFU].

IRs and IRRs of different clinical event categories between individuals with a persistent CXCR4-tropism and other tropisms (persistent CCR5-tropism or dual-mixed tropism) are reported in Table 2.

People living with four-class drug-resistant HIV with persistent CXCR4-tropic virus had higher IRs of HIV-related infections, HIV-related events and AIDS-defining events compared to individuals with persistent CCR5-tropic virus or a dual-mixed tropism, with an IRR of 2.4 (95% CI = 1.2–4.9, $P = 0.01$), 2.1 (95% CI = 1.1–3.9, $P = 0.02$) and 2.3 (95% CI = 0.9–5.4, $P = 0.05$), respectively (Table 2).

After adjusting for age, sex at birth and CD4+/CD8+ ratio at baseline, standardized viremia copy-years [adjusted-IRR: 1.66 (95% CI = 1.2–2.3), $P < 0.001$] and persistent CXCR4-tropism [adjusted-IRR: 2.01 (95% CI = 1.0–3.9), $P = 0.037$] were associated with the occurrence of HIV-related events.

Discussion

Our results show that 4DR-PWH with persistent CXCR4-tropic virus have higher IRs of HIV-related infections, HIV-related

Table 1. Baseline characteristics, according to HIV-co-receptor tropism, of 4DR-PWH with at least two tropism determinations

Baseline characteristics	Overall ($n=144$)	Dual-mixed or CCR5-tropism ($n=97$)	Persistent CXCR4 ($n=47$)	*P* overall
Sex at birth (male)	110 (76.4%)	71 (73.2%)	39 (83.0%)	0.277
Age (years)	49.8 (44.2–53.6)	50.3 (45.8–53.6)	49.1 (42.7–54.1)	0.571
Risk factor HIV				0.503
Other	39 (27.1%)	24 (24.7%)	15 (31.9%)	
MSM	43 (29.9%)	27 (27.8%)	16 (34.0%)	
TD	36 (25.0%)	27 (27.8%)	9 (19.1%)	
HCV and/or HBV coinfection	41 (28.5%)	25 (25.8%)	16 (34.0%)	0.404
Years since HIV diagnosis	21.3 (17.7–26.0)	21.9 (16.9–26.6)	20.6 (18.1–23.2)	0.084
Years of ART	18.2 (14.5–21.4)	18.3 (14.8–21.8)	18.0 (13.6–20.6)	0.563
Detectable HIV-RNA	132 (93.0%)	91 (95.8%)	41 (87.2%)	0.115
HIV-RNA (copies/mL)	2402 (186–21321)	3382 (342–17686)	568 (140–43690)	0.534
Nadir CD4+ (cells/mm^3)	80.0 (17.5–190)	105 (29.5–201)	45.0 (10.0–160)	0.098
CD4+ (cells/mm^3)	388 (191–600)	408 (204–600)	329 (184–576)	0.455
CD8+ (cells/mm^3)	974 (615–1316)	956 (682–1288)	1008 (604–1436)	0.792
CD4+/CD8+	0.36 (0.2–0.7)	0.37 (0.2–0.7)	0.29 (0.2–0.6)	0.482

Results described by median (IQR) or frequency (%) and compared by Mann–Whitney or χ^2/Fisher's tests.

events and AIDS-defining events compared to individuals with persistent CCR5-tropic virus or dual-mixed tropism, even in the modern ART era.

These findings can appear in line with the results brought up in a retrospective cohort study conducted in London in 2007,[2] although, in this study, only people with a naïve infection at the time of first HIV-tropism determination were included.

In 2008, a subset of the Swiss HIV Cohort Study on PWH who initiated ART between 1995 and 1998 revealed similar results to our study, demonstrating how people with a CXCR4-tropic virus are characterized by a higher probability of progressing to AIDS or death, despite ART.[7]

Moreover, a longitudinal study from the Multicenter AIDS Cohort Study showed how CXCR4-tropic virus and dual-mixed tropism are associated with the development of AIDS.[8]

In our study, 33% of 4DR-PWH had a persistent CXCR4-tropism; this percentage is higher than the one highlighted in the EXPLORE study, where only 3.2% of tested men had CXCR4-using HIV-1 strains.[9] It has to be emphasized that the EXPLORE study only considered men who have sex with men with a recent HIV-1 infection diagnosis. The difference between these two studies can be explained by the fact that in our study, people are characterized by a four-class drug-resistant HIV, while in the EXPLORE study, only 16% of PWH had evidence of resistance to at least one antiretroviral drug, and 1.5% of individuals had a documented resistance to three drug classes.[9]

However, our percentage is in line with that evidenced in the Multicenter AIDS Cohort Study, where 52% of men included in the study showed a CXCR4-tropic virus at any of the time points tested.[10]

We did not find any statistically significant difference in clinical and immunovirological characteristics at baseline between 4DR-PWH with a persistent CXCR4-tropic virus when compared to other individuals (with a persistent CCR5-tropic virus or a dual-mixed tropism). This finding is similar to a study conducted in France between 1995 and 2008,[11] although this study monitored the biological and clinical outcomes of individuals with a primary HIV infection, and they compared individuals with a persistent CCR5-tropic virus with PWH characterized by a dual-mixed tropism.

Today, it is known that CXCR4-tropic viruses can evolve from pre-existing CCR5-tropic viruses[10]; this, in addition to the extensive history of ART failure, could explain the high percentage of individuals with a persistent CXCR4-tropic virus in our study, given the median time since HIV diagnosis of 21.3 years.

Today, it has been largely demonstrated how cumulative HIV replication is associated with all-cause mortality, causing damage independent of simultaneous immunodeficiency[12]; this could partially explain why, in our study, in addition to persistent CXCR4-tropism, standardized viremia copy-years was associated with the occurrence of HIV-related events.

It has to be highlighted that in our cohort, 27% of individuals had persistent CCR5-tropism, which gives the opportunity to use CCR5 inhibitors as an alternative therapeutic strategy for this difficult-to-treat population.

This study has some limitations that need to be mentioned. First, the only HIV-co-receptor tropism determinations available were from the date of the first four-class drug resistance evidence; we do not have data on previous tropism. Second, the Geno2Pheno algorithm may misclassify dual-mixed or borderline cases, potentially under- or overestimating CXCR4 usage, though it remains a widely accepted genotypic tropism prediction tool. Third, the study design was retrospective. Finally, the sample size of 4DR-PWH can appear limited, but to our knowledge, this is the first study on the occurrence of clinical events according to HIV-co-receptor tropism in this fragile population and incorporating such an extended follow-up.

Table 2. IRs and IRRs of different clinical event categories between persistent CXCR4-tropism and other tropisms (persistent CCR5 or tropism switch), in 4DR-PLWH with at least two tropism determinations

Clinical events	Number of PWH with persistent CXCR4	Number of events in people with persistent CXCR4	IR (95% CI) in people with persistent CXCR4 per 100-PYFU	Number of people with dual-mixed or CCR5-tropism	Number of events in people with dual-mixed or CCR5-tropism	IR (95% CI) in people with other tropism per 100-PYFU	IRR (persistent CXCR4/other tropism), 95% CI	*P*-value
Overall events	37	124	32.5 (27.1. 38.8)	80	257	32.4 (32.4, 36.7)	1.00 (0.81, 1.24)	0.975
Deaths	9	9	2.36 (1.08, 4.48)	10	10	1.26 (0.60, 2.32)	1.87 (0.76, 4.61)	0.165
HIV-related infections[a]	10	16	4.2 (2.4–6.82)	11	14	1.77 (0.97–2.96)	2.38 (1.16–4.87)	0.010
Non-HIV-related infections	11	22	5.77 (3.62–8.74)	36	62	7.83 (6–10.03)	0.74 (0.45–1.2)	0.220
MACE[b]	4	4	1.05 (0.29–2.69)	11	16	2.02 (1.15–3.28)	0.52 (0.17–1.56)	0.230
Virus-related malignancies[c]	4	4	1.05 (0.29–2.69)	7	7	0.88 (0.36–1.82)	1.19 (0.35–4.06)	0.780
Not virus-related malignancies	4	4	1.05 (0.29–2.69)	6	7	0.88 (0.36–1.82)	1.19 (0.35–4.06)	0.780
AIDS-defining events	5	11	2.89 (1.44–5.17)	8	10	1.26 (0.61–2.32)	2.29 (0.97–5.39)	0.050
HIV-related clinical events[d]	10	20	5.25 (3.21–8.11)	15	20	2.52 (1.54–3.9)	2.08 (1.12–3.86)	0.020

PYFU, person-years of follow-up; 95% CI, confidence interval 95%.

[a]HIV-related infections: all infections included in the categories B and C of CDC 1993 classification.

[b]Major adverse cardiac events (MACE) include myocardial infarction, unstable angina, stroke, transient ischaemic attack, peripheral arterial ischaemia and revascularization.

[c]Virus-related malignancies include anal and cervical cancer, Kaposi's sarcoma, Hodgkin's disease and high-grade non-Hodgkin lymphoma and hepatocarcinoma.

[d]HIV-related events: all conditions included in the categories B and C of CDC 1993 classification.

Conclusions

The current study showed that 33% of 4DR-PWH had a persistent CXCR4-tropic virus, and it evidenced how a persistent CXCR4-tropic virus, together with standardized viremia copy-years, in the modern ART era, continues to be associated with an increased risk of HIV-related infections, HIV-related events and AIDS-defining events, even when adjusted for age, sex at birth and CD4+/CD8+ ratio at baseline.

Our findings expand knowledge on the clinical effect of HIV-co-receptor tropism and confirm CXCR4-tropism as a marker of HIV progression also in the 4DR population, suggesting the need of further prioritization of viro-immunological control and studies of pathogenic mechanisms in the presence of CXCR4-tropic multidrug-resistant viral strains.

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Author contributions

R.P.B., V.S. and A.C. conceived the study. S.D. and R.L. performed statistical analysis. R.P.B, S.D. and V.S. interpreted the findings. R.P.B. drafted the manuscript, with the support of S.D., V.S. and R.L. who reviewed the manuscript. G.C., L.C., A.C., A.S., T.C., M.M., S.L, D.A. and M.M.S. helped with data acquisition and reviewing the manuscript. A.C. coordinated clinical activities and was involved in revising the manuscript for important intellectual content. All the authors read and approved the final manuscript.

Supplementary data

Table S1 is available as Supplementary data at *JAC* Online.

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