

Large decrease in the proportion of newly diagnosed HIV-1 infections grouping in large clusters in Spain

Michael M Thomson^{1*}, Horacio Gil¹, Sonia Benito¹, María Moreno-Lorenzo¹, Mónica Sánchez¹, Javier E. Cañada-García¹, Elena Delgado¹, and the Spanish Group for the Study of New HIV Diagnoses

¹HIV Biology and Variability Unit, Centro Nacional de Microbiología, Instituto de Salud Carlos III. Majadahonda, Madrid, Spain

*E-mail: mthomson@isciii.es

Background:

In recent years, increasing HIV-1 phylogenetic clustering has been observed in many countries, including Spain, frequently associated with men who have sex with men (MSM). The use of phylogenetic methods has been advocated for the detection of large or rapidly growing HIV-1 clusters, to assist in prioritizing preventive interventions were they would be expected to be more effective, and to monitor their efficacy. Here we longitudinally analyze HIV-1 clustering in a large Spanish cohort of newly diagnosed infections in the years before and after the roll-out of pre-exposition prophylaxis (PrEP) in December 2019.

Methods:

HIV-1 protease-reverse transcriptase (PR-RT) was amplified by RT-PCR using RNA extracted from plasma from HIV-1 infections newly diagnosed Spain in 2017-2022 in clinical centers from 13 regions. Phylogenetic analyses were performed with the approximate maximum likelihood method implemented in FastTree2, including more than 15,000 HIV-1 PR-RT sequences from samples collected in Spain in 1999-2023. Clusters were defined as those supported by SH-like values ≥ 0.95 comprising ≥ 4 individuals, at least 50% of them native Spaniards, with large clusters being defined as those comprising ≥ 30 individuals. In 6.4% patients, only integrase and/or env V3 sequences were obtained, which were used for phylogenetic analyses. Statistical analyses were performed with Fisher's exact test.

Results

Sequences were obtained from 3,204 patients newly diagnosed of HIV-1 infection in 2017-2022, 60.2% of whom were self-declared MSM (Fig. 1). Each year 54.9-64.8% infections grouped in clusters of ≥ 4 individuals, without statistically significant annual changes (Fig. 2). However, when only large clusters, comprising ≥ 30 individuals ($n=29$, 25 of which were associated with MSM), were considered, a decrease was observed in the proportion of newly diagnosed infections belonging to them from 16%, 13.7%, 14.8%, 17.3%, and 17.8% in successive years 2017-2021 to 11.5% in 2022 (Fig. 3), a reduction which was statistically significant in 2022 compared to 2021 ($p=0.0064$) and to the aggregate data of 2017-2021 ($p=0.019$). No other statistically significant annual change in the proportion of new HIV-1 diagnosis grouping in large clusters was observed during the period 2017-2022. Decreases from 2021 to 2022 were observed in the 3 regions contributing with ≥ 30 new HIV-1 diagnoses each year (Madrid, Basque Country, and Galicia) (Fig. 4), with those in Madrid and Galicia being statistically significant ($p=0.0039$ and 0.0007 , respectively) and that in Basque Country being marginally nonsignificant ($p=0.075$). Considering the 4 largest clusters individually (each comprising ≥ 100 individuals), decreases in the proportion of infections grouping in large clusters from 2021 to 2022 were observed in all of them (Fig. 5), although the only statistically significant reduction was in A1_1, with a significant reduction from 2020 to 2022 also observed in F1_1.

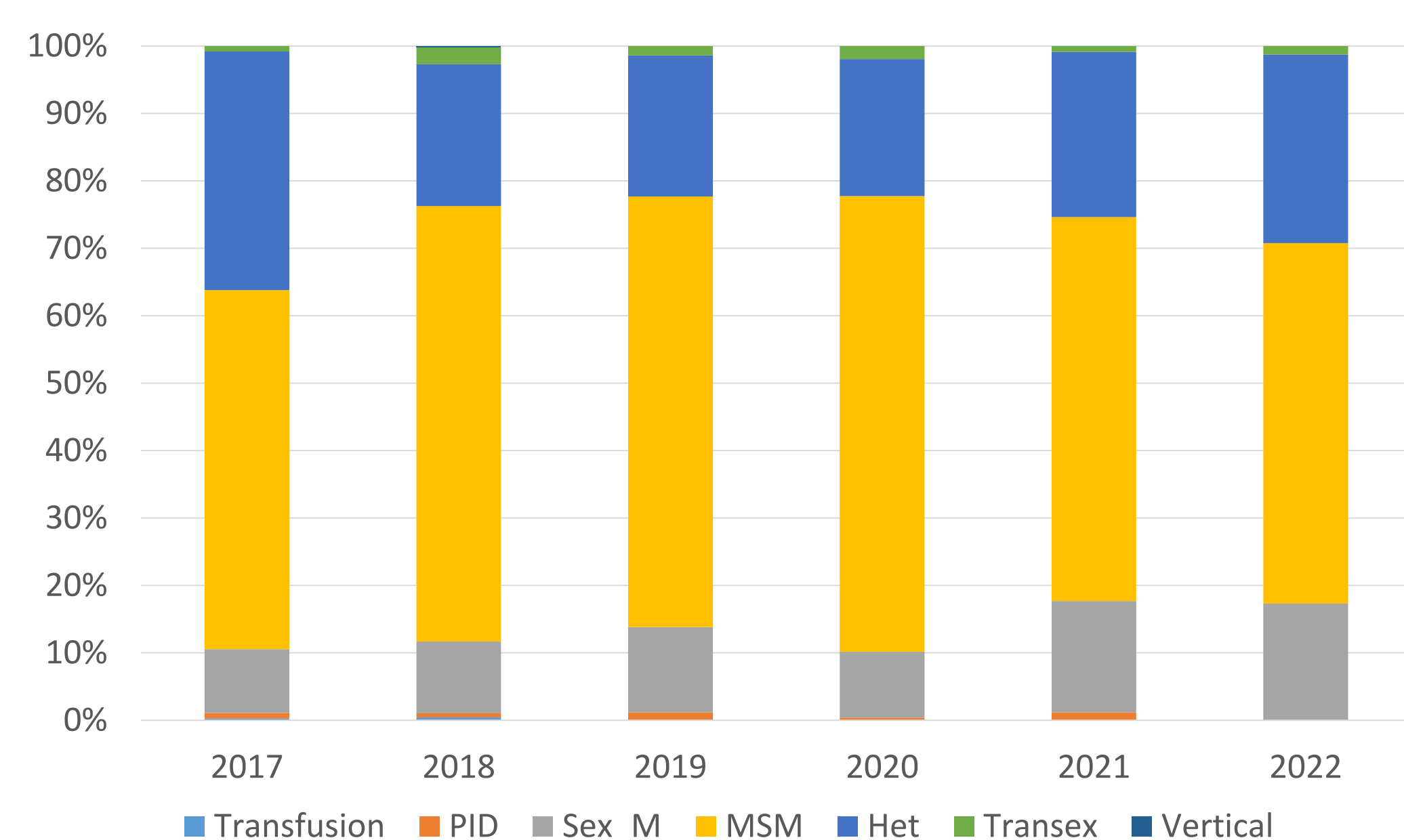


Fig. 1. Transmission route in new HIV-1 diagnoses in the study cohort. Only data from patients with known transmission route were used for the graph. PID: persons who inject drugs; MSM: men who have sex with men; Het: heterosexual; Sex_M: unspecified sexual transmission in male patient; Transex: transexual patient.

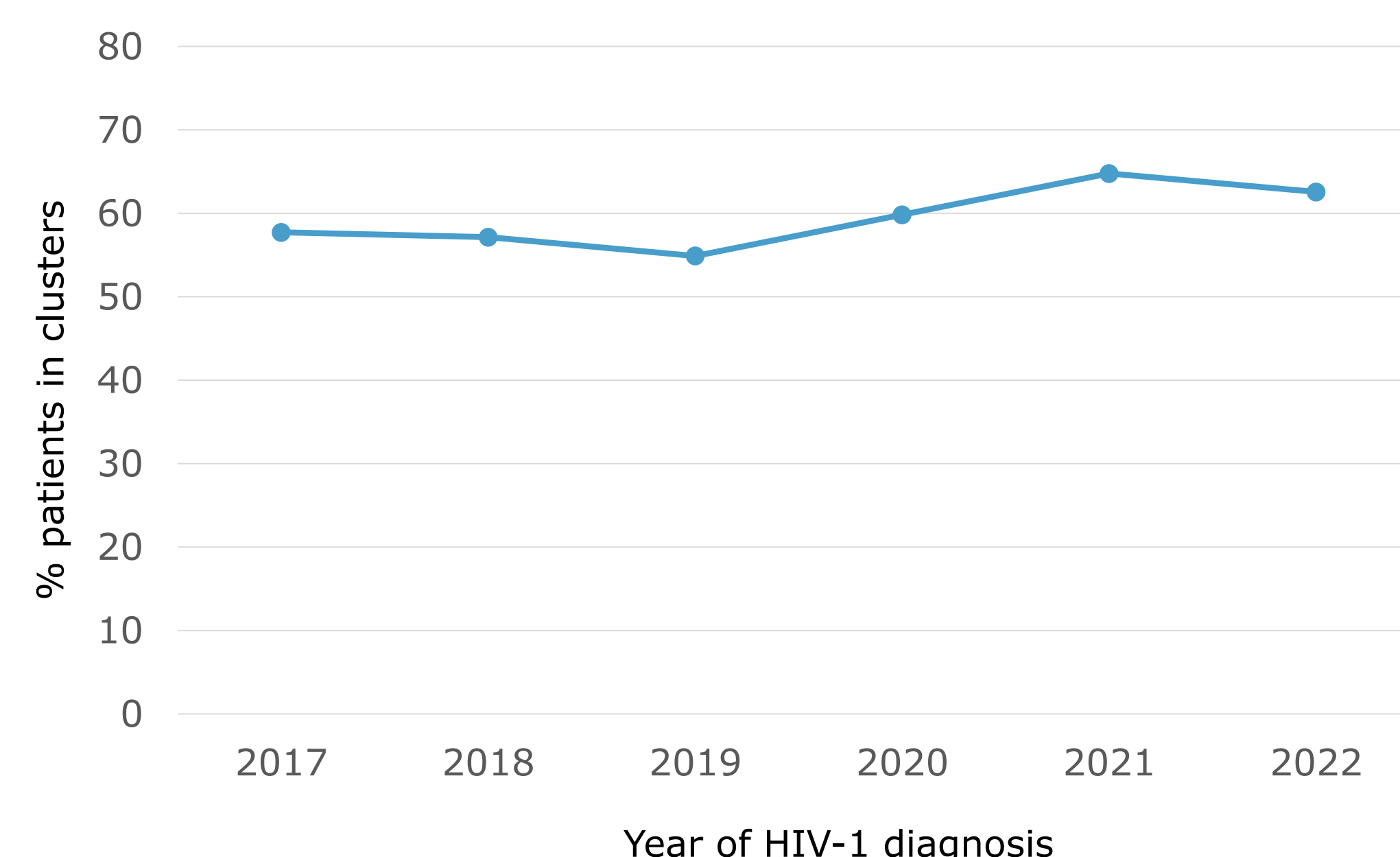


Fig. 2. Proportion of new HIV-1 diagnoses belonging to clusters of 4 or more individuals according to year of diagnosis. The annual differences were statistically nonsignificant.

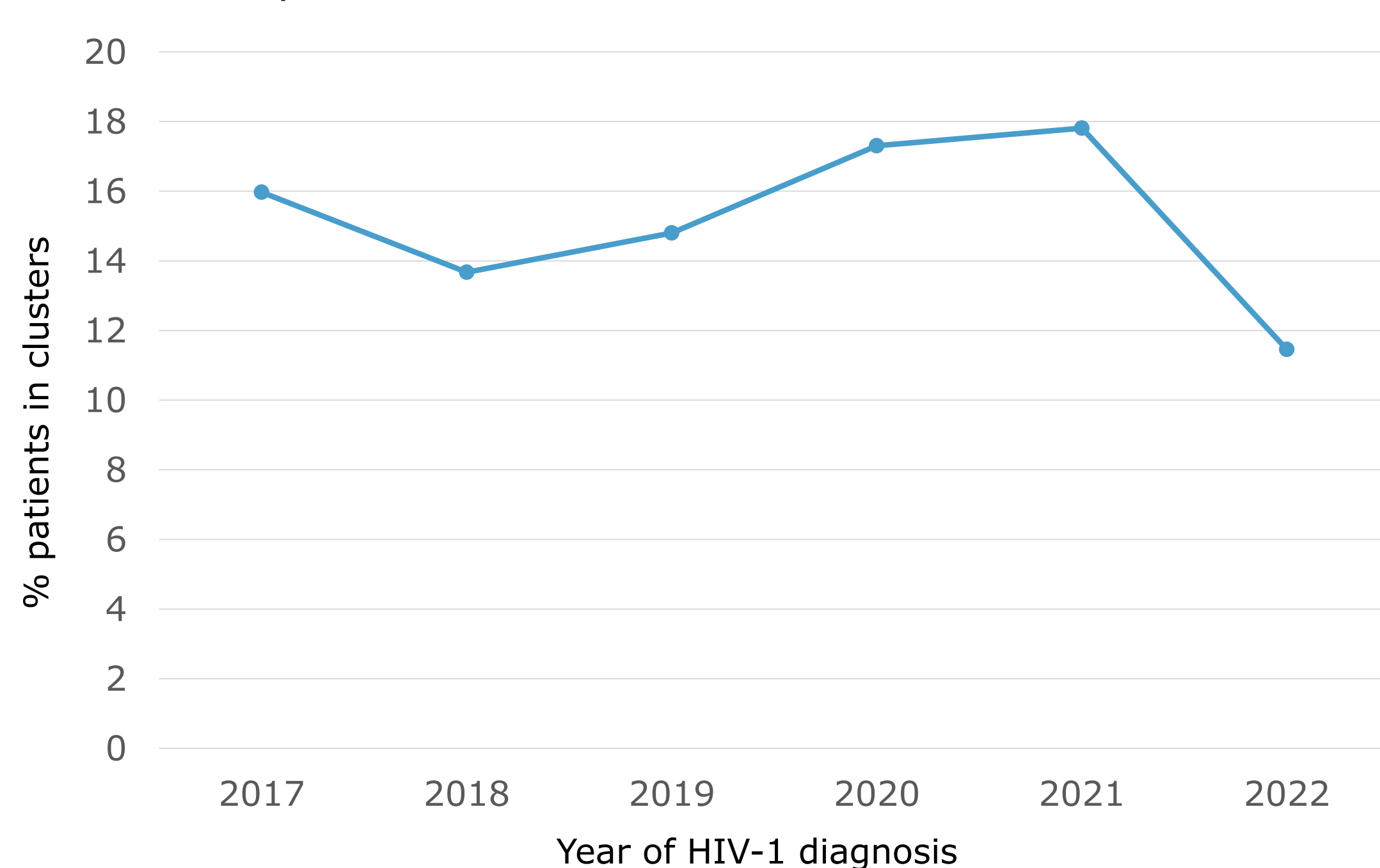


Fig. 3. Proportion of new HIV-1 diagnoses in large clusters (of 30 or more individuals), according to year of diagnosis. The decrease in 2022 compared to 2021 (46.7%) and to the aggregate 2017-2021 diagnoses (26.8%) was statistically significant.

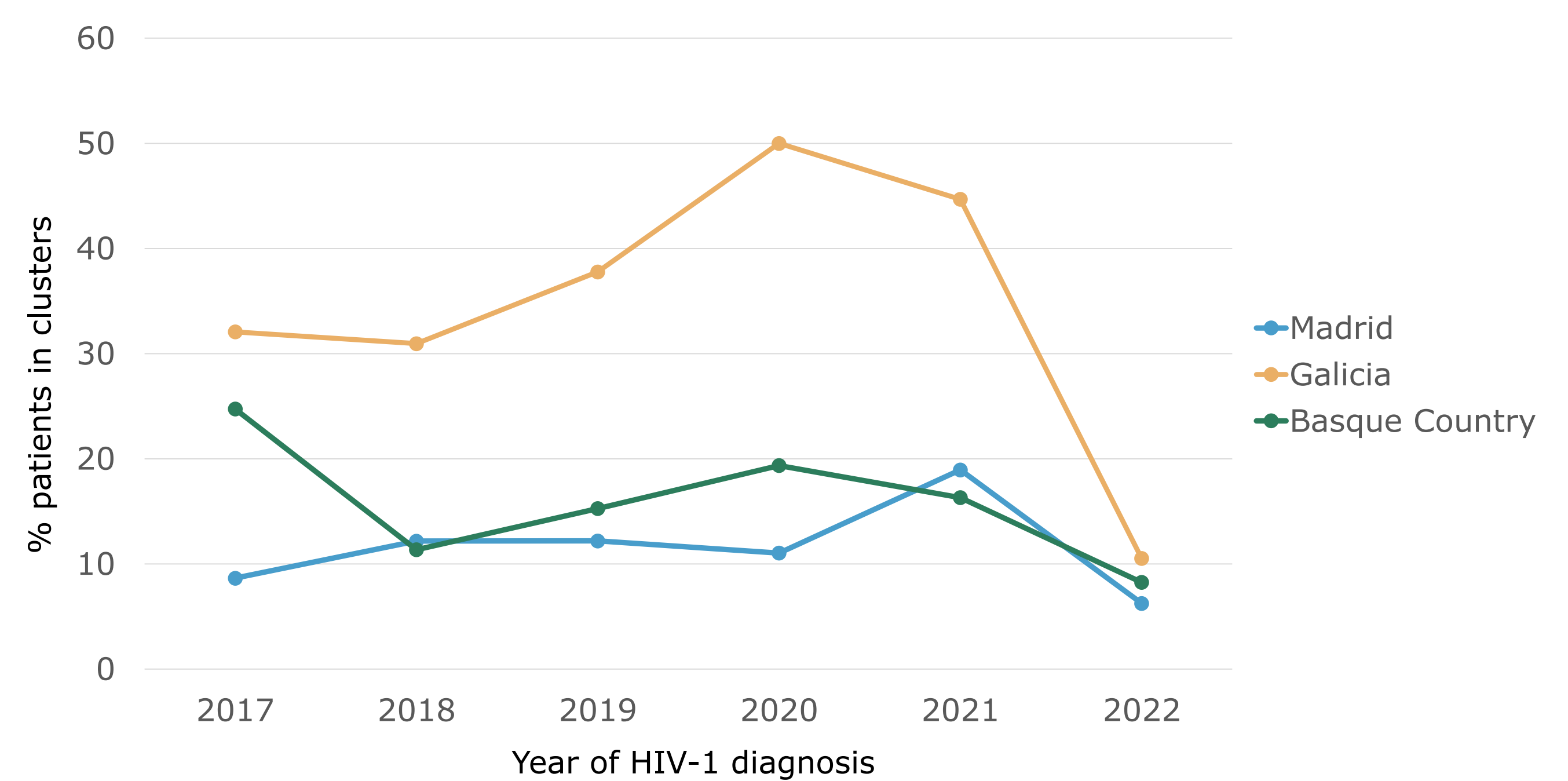


Fig. 4. Proportions of new HIV-1 diagnoses in large clusters (of 30 or more individuals), according to year of diagnosis, in the regions of Madrid, Galicia, and Basque Country. Decreases from 2021 to 2022 of 67%, 76.4%, and 49.4%, respectively, were observed. The decreases were statistically significant in Madrid and Galicia.

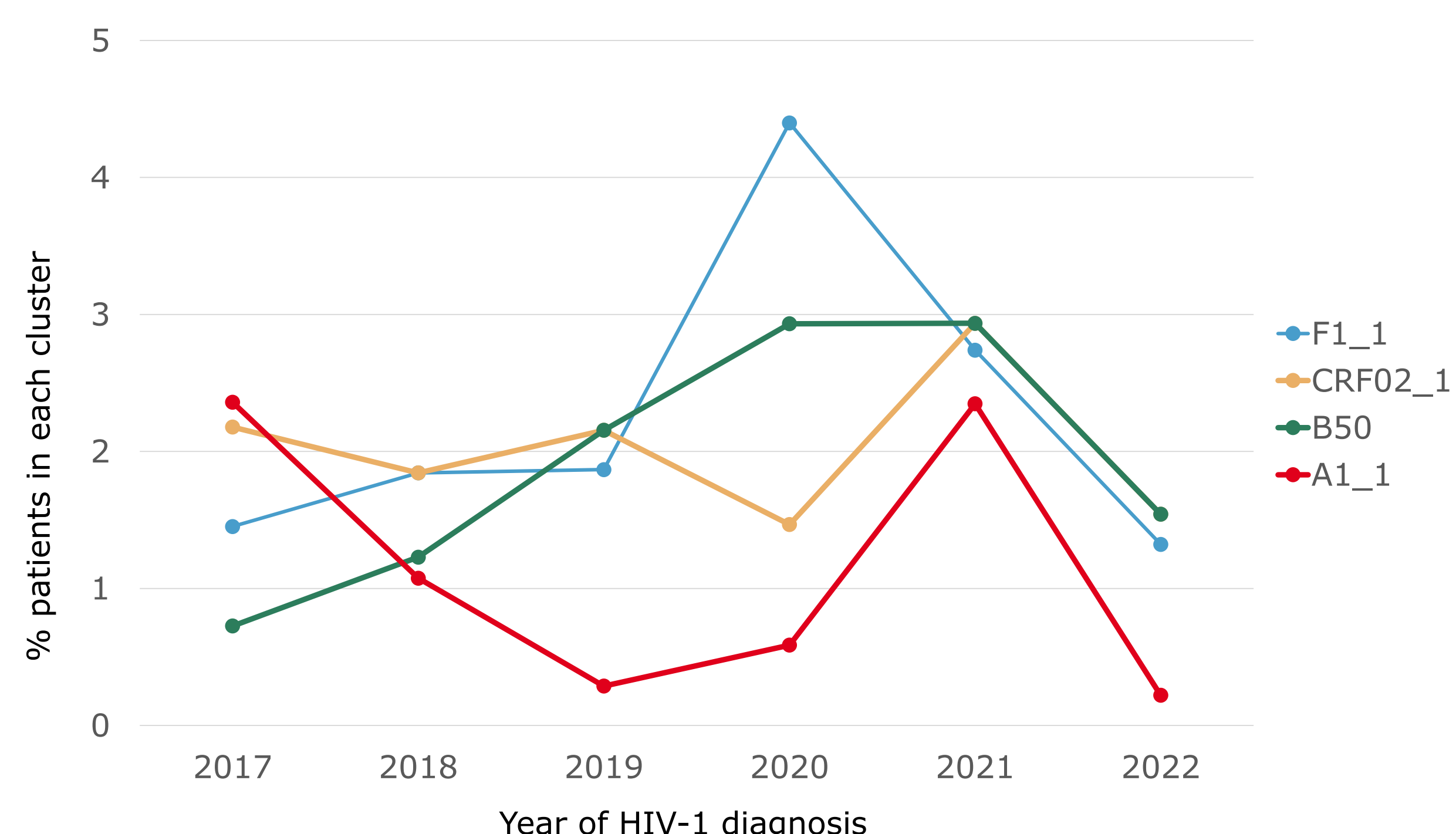


Fig. 5. Proportions of new HIV-1 diagnoses in the 4 largest clusters, of ≥ 100 individuals, according to year of diagnosis. Decreases were statistically significant from 2021 to 2022 in A1_1 and from 2020 to 2022 in F1_1. All 4 clusters are associated with MSM.

Conclusions and discussion

- A statistically significant decrease in the proportion of HIV-1 infections newly diagnosed in Spain in 2022 belonging to large (≥ 30 individuals) clusters was observed, compared to infections diagnosed in previous years.
- Since such decrease was observed 2 to 3 years after roll-out of PrEP in Spain, and was consistent in different regions and clusters, a causal correlation is proposed. The delay since PrEP roll-out could be due to its slow start and gradual implementation. It could be speculated that the greater effect of PrEP on large clusters relates to the fact that such clusters reflect transmission networks presumably associated with MSM with multiple sexual partners engaging in unprotected sexual intercourse, who are the major users of PrEP. The proposed causal relation would be reinforced if a similar phenomenon is observed in other countries where PrEP programs have been implemented and large clusters have been identified. If such correlation is confirmed, large clusters could be used as markers to monitor the efficacy of PrEP at a population level.

Acknowledgments

- We thank the personnel at the Genomic Unit, Instituto de Salud Carlos III, for technical assistance in sequencing.
- This work was funded through Acción Estratégica en Salud Intramural (AESI), Instituto de Salud Carlos III, projects PI16CIII/00033, PI19CIII/00042, and PI22CIII/00065, and through scientific agreements with Consellería de Sanidade, Government of Galicia, Spain, and Osakidetza-Servicio Vasco de Salud, Government of Basque Country, Spain.