PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort profile: PRESTIGIO, an Italian prospective registry-based cohort of people with HIV-1 resistant to reverse transcriptase, protease, and integrase inhibitors
AUTHORS	Clemente, Tommaso; Galli, L; Lolatto, Riccardo; Gagliardini, Roberta; Lagi, Filippo; Ferrara, Micol; Cattelan, Anna Maria; Focà, Emanuele; Di Biagio, Antonio; Cervo, Adriana; Calza, Leonardo; Maggiolo, Franco; Marchetti, Giulia; Cenderello, Giovanni; Rusconi, Stefano; Zazzi, Maurizio; Santoro, Maria-Mercedes; Spagnuolo, V; Castagna, Antonella

VERSION 1 – REVIEW

REVIEWER	Sonnerborg, Anders Division of Infectious Diseases, Department of Medicine Huddinge, Karolinska Institutet and Division of Clinical Microbiology, Department of Laboratory Medicine, Karolinska Institute, Medicine Huddinge
REVIEW RETURNED	02-Nov-2023

GENERAL COMMENTS	Thanks for well-written description of an important cohort. I have the following questions/comments. I cannot see that it is stated which kind of quality control there is of the data transferred to the database (clinical and sequence information). It would of interest to know why a significant proportion of the subjects donot have integrase sequences available (method not available?). I am somewhat surprised about the very high proportion of subtype B patients (92.6%). It could be of value to discuss the reasons and the limitations of this fact for the representativeness of the cohort. In parallel with this the vast majority of patients included are born in Italy. This may also be a limitation. How come that so few patients born outside Italy are included - could be of interest to discuss this.

REVIEWER	Imaz, Arkaitz University of Barcelona
REVIEW RETURNED	08-Nov-2023

GENERAL COMMENTS	Since 4 drug-resistant HIV is uncommon, a nationwide cohort including all PLWH with these characteristics is a very important project that can provide very important information about these extremely hard-to-treat individuals with very scarce therapeutic options. The article provides comprehensive information about the cohort, the main results of the studies that have been carried out so far, and future research projects. All the information is presented clearly. I have some minor comments: Page 7: the authors state that to be included in the cohort

	participants can either sign a specific informed consent or opt out. Who decides the kind of consent? Is this an investigator's decision? Can be different for different participants? Please clarify. Page 7, line 54. The information about study population is updated on 14th March 2023. As the paper is being reviewed more than 6 months later, these data could be updated. Page 8: Study population. In addition to the general information of the participants included in the cohort it could be of interest to provide information about the median time of follow up after the inclusion in the cohort. Page 8: information about cumulative data from genotypic resistance testing. It could be of interest whether sanger or NGS is used. Is it the same for all centers? If NGS, which percentage of detection is considered of clinical significance for each ARV class?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Prof. Anders Sonnerborg, Division of Infectious Diseases, Department of Medicine Huddinge, Karolinska Institutet and Division of Clinical Microbiology, Department of Laboratory Medicine, Karolinska Institute
Comments to the Author:
Thanks for well-written description of an important cohort. I have the following questions/comments. I cannot see that it is stated which kind of quality control there is of the data transferred to the database (clinical and sequence information).

I would like to thank the Reviewer for this comment. We have added some details in the "Cohort description - Cohort variables and electronic case report form" section about the quality control, which is multi-level for the Registry:

- the electronic case report form (eCRF) has several automated control mechanisms (e.g., the time difference between a visit and the date of tests associated with that visit cannot be >6 months);
- a Statistical and Monitoring Team [consisting of two statisticians from the coordinating center and a data manager from the coordinating center] verifies the appropriateness and completeness of the information provided and finally requests clarifications from the staff responsible for data collection through queries on the eCRF platform;
- in case of doubt about the adequacy and completeness of the virological information, a Virology Team [composed of 2 virologists from University of Siena, 1 from University of Rome "Tor Vergata", 1 from Saint Camillus International University of Health Sciences and a Bachelor of Science from the coordinating center] is involved and queries are made via the eCRF platform.

To date, data monitoring has been performed online. Since 2024, the PRESTIGIO Registry has planned to undertake annual on-site monitoring to check source documents and data entry on a regular basis.

It would of interest to know why a significant proportion of the subjects do not have integrase sequences available (method not available?).

As suggested by the Reviewer, we have now specified that the reason why 54 (23.6%) people living with 4-class drug-resistant HIV had no available integrase genotype relies on the fact that the method was not available in all participating centers at the time of virological failure to an INSTI-containing regimen.

I am somewhat surprised about the very high proportion of subtype B patients (92.6%). It could be of value to discuss the reasons and the limitations of this fact for the representativeness of the cohort.

In parallel with this the vast majority of patients included are born in Italy. This may also be a limitation. How come that so few patients born outside Italy are included - could be of interest to discuss this.

The issues raised by the Reviewer are relevant and closely related. In a large Italian cohort of newly diagnosed HIV infections between 1997 and 2018, 80.1% of individuals were Italian and 73.1% had a B subtype virus [*Fabeni L, Santoro MM, Lorenzini P, Rusconi S, Gianotti N, Costantini A, Sarmati L, Antinori A, Ceccherini-Silberstein F, d'Arminio Monforte A, Saracino A, Girardi E, On Behalf Of The Icona Foundation Study Cohort. Evaluation of HIV Transmission Clusters among Natives and Foreigners Living in Italy. Viruses. 2020 Jul 23;12(8):791. doi: 10.3390/v12080791*]. However, the proportion of non-B subtypes has increased markedly in recent years, mainly (but not exclusively) attributable to non-Italian natives [*Rossetti B, Di Giambenedetto S, Torti C, Postorino MC, Punzi G, Saladini F, Gennari W, Borghi V, Monno L, Pign ataro AR, Polilli E, Colafigli M, Poggi A, Tini S, Zazzi M, De Luca A; Antiviral Response Cohort Analysis (ARCA) Collaborative Group. Evolution of transmitted HIV-1 drug resistance and viral subtypes circulation in Italy from 2006 to 2016. HIV Med. 2018 Oct;19(9):619-628. doi: 10.1111/hiv.12640*].
Although the PRESTIGIO Registry is characterized by a currently open recruitment, people living with 4-class drug-resistant HIV are usually characterized by a long antiretroviral treatment (ART) duration with multiple virological failures and heavy treatment experience. Actually, in our cohort the median duration of HIV infection (until 14th March 2023) was 29.8 (25.3-33.7) years, with ART initiation before 1998 in the majority of cases [148 (64.6%)]. This could at least partially justify the high proportions of Italian natives (91.7%) and subtype B (92.6%); it is possible that in the coming years, following the trend of newly diagnosed infections, non-Italian natives and subtype non-B viruses with 4-class drug resistance could be included in the registry. We have included these aspects in the “Strengths and limitations of this study” and in the “Strengths and limitations” sections.

Reviewer: 2
Dr. Arkaitz Imaz, University of Barcelona
Comments to the Author:
Since 4 drug-resistant HIV is uncommon, a nationwide cohort including all PLWH with these characteristics is a very important project that can provide very important information about these extremely hard-to-treat individuals with very scarce therapeutic options.
The article provides comprehensive information about the cohort, the main results of the studies that have been carried out so far, and future research projects. All the information is presented clearly.
I have some minor comments:
Page 7: the authors state that to be included in the cohort participants can either sign a specific informed consent or opt out. Who decides the kind of consent? Is this an investigator’s decision? Can be different for different participants? Please clarify.

I wish to thank the Reviewer for this question which has allowed us to correct the “Cohort description - Study design” section. In particular, we have removed the word “specific” because the consent was the same for all centers and all participants.

Page 7, line 54. The information about study population is updated on 14th March 2023. As the paper is being reviewed more than 6 months later, these data could be updated.

The issue raised by the Reviewer is important. However, the data collection and subsequent verification by the statistical and monitoring team is done on an annual basis (as specified in the “Cohort description - Study design” section) and the update is performed in January (so next update will be in January 2024), with verification by March 2024.

Page 8: Study population. In addition to the general information of the participants included in the cohort it could be of interest to provide information about the median time of follow up after the inclusion in the cohort.

We thank the Reviewer for this comment. As stated in the “Cohort description - Study design” section, we consider follow-up from the first evidence of 4-class drug resistance until death, loss to follow-up, or patient’s withdrawal of the consent. Therefore, the median follow-up time was already reported in

Table 2 as “Years since evidence of 4-class drug resistance” [7.7 (4.8 - 10.2) years]. Now we have now clarified this both in Table 2 and in the “Cohort description - Study population” section.

Page 8: information about cumulative data from genotypic resistance testing. It could be of interest whether sanger or NGS is used. Is it the same for all centers? If NGS, which percentage of detection is considered of clinical significance for each ARV class?

According to the Reviewer’s comment, we have specified in the “Cohort description - Study population” section that we currently have only Sanger sequencing data in the Registry; NGS has only been used only for research purposes. However, the registry eCRF has been modified to receive also capsid and envelope sequencing data, as well as data from NGS, from every center where they are available.