Factors associated with late presentation for HIV care in a single Belgian reference center: 2006–2017

Gilles Darcis¹, Iseult Lambert¹, Anne-Sophie Sauvage¹, Frédéric Frippiat¹, Christelle Meuris¹, Françoise Urlings¹, Marianne Lecomte¹, Philippe Léonard¹, Jean-Baptiste Giot¹, Karine Fombellida¹, Dolores Vaira² & Michel Moutschen¹,²

Late presentation for HIV care is a major issue and the cause of higher morbidity, mortality and transmission. In this regard, we analyzed the characteristics of patients presenting for care at our center from January 2006 to July 2017 (n = 687). The majority of the studied population was of African origin (54.3%) with heterosexual women representing the main group (n = 292; 42.5%). 44% of the patients were late presenters (LP) (presenting for care with CD4 T cells <350/mm³ or an AIDS defining event) and 24% were late presenters with advanced disease (LP-AD) (presenting for care with CD4 T cells <200/mm³ or an AIDS defining event). A very high risk of being LP and LP-AD was associated with Sub-Saharan origin (OR 3.4 and 2.6 respectively). Other factors independently associated with LP or LP-AD were age (OR 1.3), male gender (OR 2.0 and 1.5 respectively) and heterosexual route of transmission (OR 2.4 and 2.3 respectively). A significant increase in HIV screening without forgetting those groups would contribute to earlier HIV diagnosis, a key element to end the HIV epidemic. To achieve this goal, addressing the specific hurdles to HIV testing in the migrant population is critical.

Since a few years, the 90-90-90 target has become a central column of the worldwide pursuit to end the AIDS epidemic. The target reflects a fundamental shift in the world's approach to HIV treatment towards the importance of maximizing viral suppression among people living with HIV¹. Antiretroviral therapy (ART) is now recommended for all those with HIV infection in order to prevent AIDS-related illness and to decrease the risk of transmission.

Late presentation (LP) for care is a significant and persistent issue for the success of ART outcomes. Indeed, late presenters have an extended chance to transmit HIV while they are unaware of their HIV infection²⁻⁵. LP is also associated with a negative impact on mortality and morbidity⁶,⁷. Regarding to immunological recovery, patients who began ART with ≤350 CD4 T cells/mm³ generally do not regain normal CD4 naïve/memory T cell ratios⁸. The START trial clearly showed that the immediate initiation of antiretroviral therapy was superior to deferral of such therapy until the CD4 T cell count declined to 350 cells/mm³⁹. A beneficial effect of immediate antiretroviral therapy was evident for both serious AIDS-related and serious non–AIDS-related events⁹, and the relative risk reduction was greatest among older participants, those with high plasma HIV RNA viral loads and with low baseline CD4 to CD8 ratios¹⁰.

Moreover, early initiation of ART restricts the establishment of the HIV reservoirs that are considered as a major barrier to the cure of HIV infection¹¹,¹². Early treatment not only reduces the size of the latent reservoir, but also alters the composition of the reservoir in a way that may enhance the efficacy of potential eradication therapies¹³. Indeed, unless ART is started early, a large majority of latent viruses which constitute the HIV reservoir carries mutations that render infected cells insensitive to cytotoxic T lymphocytes (CTL)¹³.

Because of its many negative consequences for infected individuals and HIV transmission, it is critical to identify factors associated with late presentation for HIV care. The identification of those factors could indeed improve the effectiveness of HIV testing strategies with a focus on susceptible and possibly neglected groups.

A cross-European update from 34 countries on the prevalence and factors associated with LP has recently been published¹⁴. The huge number of patients included in this study allowed for an interesting and statistically significant analysis of factors associated with LP overtime. However, it highlighted also that there are major

¹Infectious Diseases department, Liège University Hospital, Liège, Belgium. ²AIDS Reference Laboratory, Liège University, Liège, Belgium. Correspondence and requests for materials should be addressed to G.D. (email: gdarcis@chu.ulg.ac.be)
differences between European regions, reducing the usefulness of such an analysis as the aim is to adapt the local testing strategies.

In this study, we conducted a rigorous analysis of factors associated with LP and LP with advanced disease (LP-AD) in a single Belgian reference center, with the ultimate objective to improve local early screening policies as well as in countries or regions around the world sharing similar epidemiologic and demographic characteristics.

**Methods**

**Patients and definition of late presentation.** This was a retrospective cohort study. People aged at least 16 who presented for care (first clinic visit) at the Liege University Hospital (Belgium) between the 1st January 2006 and 31 July 2017 were included in the study. Patients who had already received care for their HIV infection at another clinical center were excluded from the study as well as people already treated for more than one month before the first clinic visit. According to the consensus definition of LP15, patients who were previously diagnosed but who did not access to care were kept in the analysis. Indeed, the term ‘presentation for care’ means attendance at a health care facility that is able to monitor progression of HIV infection and initiate appropriate medical care. Diagnosis of HIV infection means presentation for care only if diagnosis of HIV infection is linked to appropriate access to care16. This information was obtained based on standardized procedure used to determine medical histories at first presentation for care. Although it is not completely excluded that some patients presented for care in another center at an earlier time, we believe this approach is an effective and rigorous way to be in line with the LP definition13.

LP was defined as presentation for care with CD4 T cells < 350/μl or an AIDS defining event (at any CD4 T cell count) in the six months following first visit. LP with advanced HIV disease (LP-AD) was defined as presentation for care with CD4 T cells < 200/μl or an AIDS defining event (at any CD4 T cell count) in the six months following first visit. Seroconverters (negative HIV test over the past six months; n = 10) with CD4 T cell count < 350/μl were moved from the LP or LP-AD groups to the non-LP group. By definition, such people are diagnosed soon after HIV infection, even if they have a low CD4 T cell count at HIV diagnosis. They would not have been reached by interventions that promote earlier targeted screening. Patients infected with HIV-2 were excluded from the analyses as kinetics of CD4 T cell count decrease might be different.

Information obtained at first clinic visit included date of birth, gender and geographical origin categorized as Belgium, Sub-Saharan Africa (SSA) and other to reflect the main group of immigrants in Belgium. HIV exposure group categorized as homo-/bisexual, heterosexual, and other (including intravenous drug use (IDU)) was also collected. Participants with both sexual and IDU transmission risk (n = 5) were included in one of the sexual transmission groups.

Reported information finally included the screening context categorized as voluntary screening, medical condition, refugee (defined as a person fleeing armed conflict or persecution and asking or benefiting from assistance by the state, the Red Cross or other organizations), incidental screening (for instance before a blood donation), pregnancy, HIV+ partner or other/unknown. Information regarding AIDS-defining illnesses and CD4 T cell count at first entry into care at the HIV clinic was available and was included in the analyses.

The Ethical Committee of the University Hospital of Liège approved the study protocol (reference 2018/118). Patients were informed of data collection by their treating physician and patients could object to further collection of clinical data according to an opt-out procedure. All patients included were assigned unique identification numbers to anonymize the data and protect confidentiality. All methods were carried out in accordance with relevant guidelines and regulations16.

**Statistical analysis.** Data were summarized as median and interquartile range (IQR) and extreme values for quantitative variables while frequency tables were used for the categorical findings. Multiple logistic regression was used to identify the impact of the patients’ characteristics on late presentation. Multiple imputation was used to replace missing values. Results were considered significant at the 5% critical level (p < 0.05). Data analysis was carried out using SAS (version 9.4 for Windows). R (version 3.2.5) packages were used for the figures.

**Results**

Of 759 patients who presented for care at the Liege University Hospital (Belgium) between the 1st January 2006 and 31 July 2017, 68 were excluded because there was evidence that these people had been previously followed at another center or treated before. Patients infected with HIV-2 (n = 4) were excluded from the analyses (see Methods). The characteristics of the 687 remaining individuals who first presented for care are shown in Table 1. The median age is 34 years. 44.7% are female. The majority of the studied population is of African origin (54.3%). Heterosexual transmission was reported in 61.0% of the participants.

Among our 687 patient cohort, heterosexual women from SSA represented the main group (n = 292; 42.5%), which corresponds to the large majority of female patients (95.1%) and the heterosexual group (69.7%).

208 patients (30.3%) were Belgian men who have sex with men (MSM). Those patients represented nearly all the patients included in the homo/bisexual transmission group.

As indicated in Table 2, 44.0% of the patients were late presenters and 24.0% were late presenters with advanced disease. The variability of the LP and LP-AD percentages from one year to another, and according to the Belgian or migrant status, was not statistically significant (Fig. S1). In particular, there was no diminution of those percentages over time. Supplementary Table 1 indicates the percentages of LP and LP-AD according to patients’ characteristics. The percentages of LP and LP-AD were higher in the groups of older individuals, in the female population, in the group of patients originating from SSA, in the heterosexual transmission group as well as in the group of refugees. In contrast, those percentages were lower in the patients diagnosed following a voluntary screening.
Factors independently associated with late presentation and late presentation with advanced disease.

Figure S2 and Table 3 present the adjusted odds ratios of being LP. Age (OR 1.3 (95% CI 1.1–1.5)), male gender (OR 2.0 (95% CI 1.3–3.1)), Sub-Saharan origin (OR 3.4 (95% CI 1.9–5.9)) as well as heterosexual route of transmission (OR 2.4 (95% CI 1.4–4.1)) were factors associated with a statistically significant higher risk of being LP. Migrants from other parts of the world than SSA had also a higher risk of being LP (OR 2.3 (95% CI 1.1–4.8)). Refugees or individuals whose HIV diagnosis was made in the context of a medical condition presented a greater risk of being LP which did not reach statistical relevance.

Table 1. Characteristics of HIV patients included in the study, January 2006 to July 2017 (n = 687). SSA: Sub-Saharan Africa. SD: standard deviation. IQR: Interquartile range.

| Characteristic                  | N (%) | Median (IQR) | Extremes     |
|--------------------------------|-------|--------------|--------------|
| Age (years)                    | 687   | 34.0 (27.0–42.0) | 16.0–68.0    |
| Gender (Female)                | 307 (44.7) |       |              |
| Origin                         |       |              |              |
| Belgium                        | 238 (34.6) |       |              |
| SSA                            | 373 (54.3) |       |              |
| Others                         | 76 (11.1) |       |              |
| Mode of acquisition            |       |              |              |
| Heterosexual transmission      | 419 (61.0) |       |              |
| Homo/Bisexual transmission     | 209 (30.4) |       |              |
| Others or unknown              | 59 (8.6) |       |              |
| First CD4 T cell count          |       |              |              |
| Number/mm³                     | 687   | 386 (210–541) | 0–1772       |
| <200/mm³                       | 155 (22.6) |       |              |
| 200–350/mm³                    | 150 (21.8) |       |              |
| >350/mm³                       | 382 (55.6) |       |              |
| Context of the screening        |       |              |              |
| Incidental screening            | 45 (6.6) |       |              |
| Voluntary screening             | 72 (10.5) |       |              |
| Pregnancy                      | 20 (2.9) |       |              |
| HIV-positive partner            | 45 (6.6) |       |              |
| Medical problem                 | 198 (28.8) |     |              |
| Refugee                        | 225 (32.8) |       |              |
| Unknown                         | 82 (11.9) |       |              |

Table 2. Proportion of late presenters (LP) and late presenters with advanced disease (LP-AD) (N = 687). (a)CD4 T cells <350/mm³ or an AIDS defining event (at any CD4) in the six months following first visit. (b)With CD4 T cells <200/mm³ or an AIDS defining event (at any CD4) in the six months following first visit.

| Characteristic | Non LP | LP (a) | LP-AD (b) |
|----------------|--------|--------|-----------|
| N (%)          | 385 (56.0) | 302 (44.0) | 165 (24.0) |

Discussion

Current guidelines indicate that ART should always be recommended irrespective of the CD4 T cell count, but the lower the CD4 T count, the greater the urgency to start ART immediately17. The use of ART is recommended at any CD4 T cell count mainly in order to reduce sexual transmission, the risk of AIDS event and mother-to-child transmission of HIV9. Early ART has also the potential benefits of reducing the severity of acute symptoms, lowering the viral load set-point and HIV reservoir size, reducing viral genetic evolution and the establishment
of CTL escape mutation, decreasing immune activation and chronic inflammation and preserving immune function\(^{18,19}\). Early ART could possibly enhance post-treatment control and response to future eradication strategies\(^{20,21}\). Consequently, the importance of early ART initiation has become increasingly evident in recent years.

In this context, analyzing the factors associated with a delayed presentation for care is certainly of importance. Several large studies have recently provided important data regarding the risks of being LP and LP-AD\(^{14,22}\). However, these studies tend to erase the differences that exist between countries or regions and can potentially impact the factors associated with LP for HIV care. For instance, in our study, we showed that the majority (54.3%) of the studied population came from SSA. This particular characteristic of our cohort is certainly due to the frequent than previously thought. In a recent report by Alvarez-del Arco, the proportion of post-migration HIV acquisition was higher for Latin America and Caribbean migrants, and was also significant (45%) for people from SSA\(^{26}\). Migrant men who have acquired HIV within Europe was 63%\(^{26}\). The proportion of post-migration HIV acquisition was higher for Latin America and Caribbean migrants, and was also significant (45%) for people from SSA\(^{26}\).

Table 3. Factors associated with late presentation (LP) – Multiple logistic regression (N = 687). *Ref = Belgian. \(^{b}\)Ref = Homo/bisexual transmission. SSA: Sub-Saharan Africa. SE: standard error. CI: confidence interval. Bolded data are statistically relevant (p < 0.05).

Table 4. Factors associated with late presentation with advanced disease (LP-AD) – Multiple logistic regression (N = 687). *Ref = Belgian. \(^{b}\)Ref = Homo/bisexual transmission. SSA: Sub-Saharan Africa. SE: standard error. CI: confidence interval. Bolded data are statistically relevant (p < 0.05).
sex with men appear at particular risk of HIV acquisition post-migration as supported by the frequent acquisition of viral clades not prevalent in native countries\(^2\). In our cohort however, the majority of patients from SSA were heterosexual women who represented 42.5% of the total studied population. Interestingly, in a French report by Desgrèes-du-Lou and colleagues, it was estimated that at least 30% of HIV-infected women born in SSA acquired HIV while living in France\(^2\). More recently, Pannettier et al. showed that sub-Saharan African women living in the Paris region were regularly exposed to non-consensual sex (NCS) forced sex in their lifetimes\(^2\). They further provided evidence of an association between NCS after migration and post-migration acquisition of HIV among sub-Saharan African migrant women\(^2\). Those reports clearly highlight the need for primary prevention programs targeting these communities. Improving access to HIV testing and treatment for all infected persons, irrespective of their immigration status, could certainly impact on reducing incidence of late presentation and infection rates both within and beyond migrant communities. This would impose addressing the numerous hurdles to HIV screening and care in migrant communities, including cultural and linguistic barriers, racism and xenophobia as well as stigma from their communities\(^2\).

We further showed that age, male gender and heterosexual route of transmission are independent factors associated with LP and LP-AD. Indeed, people who are more likely to be diagnosed and to present late usually do not consider themselves as “risk categories”. HIV screening procedures basically depend on an individual's perception of his/her HIV risk. For instance, MSM have a lower risk of being LP in our analysis, most likely because they better perceive the risk of being infected by HIV.

Additionally, healthcare providers may consider HIV testing less often in individuals who are not perceived as being at high risk of HIV such as older individuals or heterosexuals, leading to missed opportunities for HIV diagnosis. High rates of missed opportunities for HIV diagnosis have previously been reported, highlighting the ongoing need for physician education on HIV testing and clinical signs suggestive of HIV infection\(^2,3\). This is particularly relevant for people aged 50 years since this group would benefit most from immediate initiation of ART as recently shown in a post-hoc subgroup analysis of the START trial\(^4,5\). Late presentation for HIV remains a key unresolved issue with severe consequences at the individual, societal and economic levels\(^6\). As underlined by our work, information campaigns and more effective HIV testing strategies are needed to shrink the inadmissibly high rates of late presentation for HIV care. All age and risk groups have to be targeted for HIV testing. Voluntary testing has to be encouraged through education campaigns targeting high prevalence groups but also neglected groups with a higher risk of LP. The education of healthcare providers should also emphasize the importance of a widespread HIV testing.

Most importantly in the context of a large population from SSA, it is critical to address the identified blocks to HIV testing and HIV care in migrant communities. This will hopefully result in improved treatment outcomes and may reduce HIV transmission, a necessary step forward a better control of AIDS epidemic.

References

1. UNAIDS. Ending AIDS: progress towards the 90–90–90 targets, http://www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf.
2. Quinn, T. C. et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. N Engl J Med 342, 921–929 (2000).
3. Fleishman, J. A., Yehia, B. R., Moore, R. D., Gebo, K. A. & Network, H. I. V. R. The economic burden of late entry into medical care for patients with HIV infection. Med Care 48, 1071–1079 (2010).
4. Lanoy, E. et al. Frequency, determinants and consequences of delayed access to care for HIV infection in France. Antivir Ther 12, 89–96 (2007).
5. Castilla, J. et al. Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. J Acquir Immune Defic Syndr 40, 96–101 (2005).
6. Smit, C., Hallett, T. B., Lange, J., Garnett, G. & de Wolf, F. Late entry to HIV care limits the impact of anti-retroviral therapy in The Netherlands. PLoS One 3, e1949 (2008).
7. May, M. T. et al. Mortality According to CD4 Count at Start of Combination Antiretroviral Therapy Among HIV-infected Patients Followed for up to 15 Years After Start of Treatment: Collaborative Cohort Study. Clin Infect Dis 62, 1571–1577 (2016).
8. Robbins, G. K. et al. Incomplete reconstitution of T cell subsets on combination antiretroviral therapy in the AIDS Clinical Trials Group protocol 384. Clin Infect Dis 48, 350–361 (2009).
9. Group, I. S. S. et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med 373, 795–807 (2015).
10. Molina, J. M. et al. Which HIV-infected adults with high CD4 T-cell counts benefit most from immediate initiation of antiretroviral therapy? A post-hoc subgroup analysis of the START trial. Lancet HIV (2018).
11. Ananworanich, J. et al. Impact of multi-targeted antiretroviral treatment on gut T cell depletion and HIV reservoir seeding during acute HIV infection. PLoS One 7, e35948 (2012).
12. Darcis, G., Van Driessche, B. & Van Lint, C. HIV Latency: Should We Shock or Lock? Trends Immunol 38, 217–228 (2017).
13. Deng, K. et al. Broad CTL response is required to clear latent HIV-1 due to dominance of escape mutations. Nature 517, 381–385 (2015).
14. Late presenters working group in, C.I.E. et al. Late presentation for HIV care across Europe: update from the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study, 2010 to 2013. Euro Surveill 20 (2015).
15. Antinori, A. et al. Late presentation of HIV infection: a consensus definition. HIV Med 12, 61–64 (2011).
16. The STROBE Statement. University of Bern, https://www.strobe-statement.org/index.php/id=strobe-home (2009).
17. European AIDS Clinical Society. Guidelines Version 8.2 - January (2017).
18. Wilson, E. M. & Sereti, I. Immune restoration after antiretroviral therapy: the pitfalls of hasty or incomplete repairs. Immunol Rev 254, 343–354 (2013).
19. Barouch, D. H. & Deeks, S. G. Immunologic strategies for HIV-1 remission and eradication. Science 345, 169–174 (2014).
20. Deeks, S. G. et al. International AIDS Society global scientific strategy: towards an HIV cure 2016. Nat Med 22, 839–850 (2016).
21. Saez-Cirion, A. et al. Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI Study. PLoS Pathog 9, e1003211 (2013).
22. Althoff, K. N. et al. Late presentation for human immunodeficiency virus care in the United States and Canada. Clin Infect Dis 50, 1512–1520 (2010).
23. Op de Coul, E. L. et al. Factors associated with presenting late or with advanced HIV disease in the Netherlands, 1996–2014: results from a national observational cohort. BMJ Open 6, e009688 (2016).
24. Helleberg, M. et al. Late presenters, repeated testing, and missed opportunities in a Danish nationwide HIV cohort. *Scand J Infect Dis* **44**, 282–288 (2012).
25. Jiang, H. et al. Gender difference in advanced HIV disease and late presentation according to European consensus definitions. *Sci Rep* **5**, 14543 (2015).
26. Alvarez-Del Arco, D. et al. High levels of postmigration HIV acquisition within nine European countries. *AIDS* **31**, 1979–1988 (2017).
27. Fakoya, I. et al. A systematic review of post-migration acquisition of HIV among migrants from countries with generalised HIV epidemics living in Europe: implications for effectively managing HIV prevention programmes and policy. *BMC Public Health* **15**, 561 (2015).
28. Desgrees-du-Lou, A. et al. Sub-Saharan African migrants living with HIV acquired after migration, France, ANRS PARCOURS study, 2012 to 2013. *Euro Surveill* **20** (2015).
29. Pannetier, J. et al. Prevalence and circumstances of forced sex and post-migration HIV acquisition in sub-Saharan African migrant women in France: an analysis of the ANRS-PARCOURS retrospective population-based study. *Lancet Public Health* **3**, e16–e23 (2018).
30. Alvarez-del Arco, D. et al. HIV testing and counselling for migrant populations living in high-income countries: a systematic review. *Eur J Public Health* **23**, 1039–1045 (2013).
31. Chin, T., Hicks, C., Samsa, G. & McKellar, M. Diagnosing HIV infection in primary care settings: missed opportunities. *AIDS Patient Care STDS* **27**, 392–397 (2013).
32. O’Connell, S., Enkelmann, J., Sadlier, C. & Bergin, C. Late HIV presentation - missed opportunities and factors associated with a changing pattern over time. *Int J STD AIDS* **28**, 814–821 (2017).
33. D’Arminio Monforte, A. et al. HIV-Infected Late Presenter Patients. *AIDS Res Treat* **2012**, 902679 (2012).

**Acknowledgements**
We thank Nathalie Maes from the Department of Biostatistics and Medico-Economic Information, University Hospital (CHU) of Liege, Belgium, who independently analyzed the data. We thank Catherine Orban, Françoise Lequarre and Philippe Caprasse for their participation to discussions. We thank the “Fonds Leon Fredericq” and the Rotary Foundation.

**Author Contributions**
G.D., I.L., D.V. and M.M. wrote the main manuscript text. G.D. prepared the figures. All authors participated to the data collection and to the interpretation of the data. All authors reviewed the manuscript.

**Additional Information**
Supplementary information accompanies this paper at https://doi.org/10.1038/s41598-018-26852-0.

**Competing Interests:** The authors declare no competing interests.

**Publisher’s note:** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2018