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SHORT COMMUNICATION

Impact of COVID-19 on HIV late diagnosis in a specialized German centre

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Abstract

Background: The ongoing COVID-19 pandemic has been impeding HIV diagnosis and treatment worldwide. Data on the impact of COVID-19 on late diagnosis (LD) in Germany are lacking. Here we present novel data of a single-centre German HIV cohort assessing LD during COVID-19.

Methods: This is a non-interventional, single-centre retrospective cohort assessing the rate of LD comparing HIV diagnoses pre-COVID-19 with those during the COVID-19 pandemic. New diagnoses between 1 January 2019 and 1 February 2020 were classified as pre-COVID-19, and diagnoses between 1 February 2020 and 1 October 2021 were classified as during COVID-19.

Results: Between 1 January 2019 and 1 October 2021, 75 patients presented with newly diagnosed HIV infection, 34 pre-COVID-19 and 41 during COVID-19. LD increased to 83% ($n = 34/41$) during COVID-19 versus 59% ($n = 20/34$) pre-COVID-19, and CDC stage C3 rose to 44% ($n = 18$) versus 27%. Hospitalization rate increased to 49% ($n = 20$) during COVID-19 versus 29% pre-COVID-19, and 12% ($n = 5$) presented with HIV-associated neurological disease, whereas none were observed in the pre-COVID-19 group. The incidence of LD ($p = 0.020$), CD4 count < 350 cells/μL ($p = 0.037$) and < 200 cells/μL ($p = 0.022$) were statistically significantly associated with the ongoing COVID-pandemic. An association with HIV transmission risk was borderline significant ($p = 0.055$).

Conclusions: Despite comparable annual rates of new HIV diagnoses, LD has been increasing during the COVID-19 pandemic, resulting in more opportunistic infections and higher hospitalization rates, possibly reflecting pandemic-related shortages in HIV testing and care facilities. Maintaining HIV testing opportunities and access to treatment during a pandemic is crucial so as not to impede WHO elimination goals and so as to prevent an increase in AIDS-related morbidity and mortality.

KEYWORDS
CD4 count, COVID-19, HIV, late diagnosis

INTRODUCTION

Late diagnosis (LD) in HIV remains a challenging problem despite widespread accessibility to diagnostic tests and combined antiretroviral therapy (cART). In Germany, about one-third of people living with HIV are diagnosed late, as defined by CD4 T-cell count < 350 cells/μL with/or without manifest AIDS-defining illness [1]. LD is known to increase morbidity and mortality in affected in-patients and, moreover, to increase healthcare costs as well as transmission risk as a result of individuals being unaware of their HIV status [2, 3]. The ongoing COVID-19 pandemic has been impeding HIV diagnosis and treatment worldwide [4].

As there has been substantial progress in decreasing the number of new HIV infections through low-threshold HIV testing, treatment as prevention (TasP) and initiation of HIV pre-exposure prophylaxis, the ongoing COVID-19 pandemic has raised major concerns in keeping the high-quality standard accessible, which is potentially increasing the rate of HIV transmissions and additionally increasing the number of HIV late diagosis.

Currently, data on the impact of COVID-19 on late diagnosis in Germany are lacking. Here we present novel data of a single-centre German HIV cohort assessing the rate and impact of late diagnosis during COVID-19.

METHODS

The study was designed as a non-interventional single-centre retrospective cohort at the University Hospital Bonn, a maximum healthcare provider with a specialized infectious disease outpatient clinic as well as an infectious disease ward. The aim was to assess the rate of LD, comparing HIV diagnoses pre-COVID-19 (PC) with those during the COVID-19 pandemic (DC). LD was defined as a first CD4 count < 350 cells/μL with or without an AIDS-defining illness at the time of HIV diagnosis. New diagnoses between 1 January 2019 and 1 February 2020 were classified as PC patients, and diagnoses between 1 February 2020 and 1 October 2021 were classified as DC patients. In addition to assessment of demographic data, mode of HIV transmission, CD4 count, HIV-RNA and concomitant opportunistic infections (OIs), the hospitalization rate and possible necessary intensive care treatment and mortality were assessed. CD4 count was assessed by flow cytometry using XN-Series (Sysmex America Inc., Lincolnshire, IL, USA) at the Institute of Clinical Biochemistry, University Hospital Bonn. Through use of the reagent Fluorocell WDF (Sysmex Europe GmbH, Norderstedt, Germany), absolute count (number/μL) and relative count (%) of CD4 and CD8 were assessed. HIV-RNA was measured with an Abbot m2000 assay, with a lower detection rate of < 40 copies/mL blood.

Statistical Analysis

Statistical analysis was performed with IBM SPSS 28. Fisher's exact, χ^2 and Mann–Whitney *U*-test were used for statistical analysis.

The study was conducted according to the Declaration of Helsinki.

RESULTS

Baseline characteristics are shown in Table 1. Between 1 January 2019 and 1 October 2021, 75 patients presented with newly diagnosed HIV infection at the University

TABLE 1 Baseline characteristics

***n* = 75**	**Pre-COVID-19 (*n* = 34)**	**During COVID-19 (*n* = 41)**
Male sex [*n* (%)]	27 (79)	32 (78)
Median age (years)	33 (range 18–71)	34 (range 18–76)
Main transmission risk		
MSM	24 (71)	21 (51)
Heterosexual intercourse	8 (24)	11 (27)
HIV diagnosis through:		
Hospital admission	10 (30)	19 (46)
Specialist care	13 (39)	13 (32)
General practitioner	9 (27)	8 (19)
Late presentation	20 (59)	34 (83)
CD4 count < 350 cells/μL	20 (59)	34 (83)
CD4 count < 200 cells/μL	14 (41)	28 (68)
CD4 nadir (median) (cells/μL)	291 (range 3–930)	118 (10–782)

Abbreviation: MSM, men who have sex with men.

Hospital Bonn, 34 PC and 41 DC. Median ages were 33 years (range 18–71) for PC presentation and 34 years (18–76) for DC presentation. The main route of transmission was men who have sex with men (MSM), which decreased from 71% ($n = 24/34$) for PC patients to 51% ($n = 21/41$) for DC patients. The rate of first diagnosis during hospital stay was found to be highest among DC patients (46%, $n = 19/41$) and was greater than among PC patients, 30% ($n = 10/33$) of whom were diagnosed during hospital admission. Diagnosis through testing at specialist care (e.g. haematologist, dermatologist, gynaecologist, infectious disease specialist) due to referral from a general practitioner was the most common diagnostic method among PC patients (39%, $n = 13/33$).

Late presentation increased to 83% ($n = 34/41$) for DC patients versus 59% ($n = 20/34$) for PC patients, and CDC stage C3 rose to 44% ($n = 18/41$) versus 27% ($n = 9/34$), respectively. Median CD4 count was 291 cells/μL (range 3–930) for PC patients and decreased to 118 cells/μL (10–782) for DC patients. Consistently, median HIV-RNA almost doubled in DC patients, with a median of 93.759 copies/mL (range 408–9110.000) versus 48.598 copies/mL (range 957–8012.596) for PC patients; 46% ($n = 19/41$) of DC patients presented with AIDS-defining illness versus 26% ($n = 9/34$) of PC patients. *Pneumocystis jirovecii* pneumonia (PJP) was the most often reported AIDS-defining illness and was found more frequently among PC (67%, $n = 6/9$) than among DC patients (37%, $n = 7/19$). The rate of hospitalization increased to 49% ($n = 20/41$) in DC patients versus 29% ($n = 10/34$) in PC patients. Thus, the proportion of patients who required intensive care treatment was higher among the PC cohort (40%, $n = 4/10$) than among the DC cohort (30%, $n = 6/20$). Interestingly, 26% ($n = 5/19$) of DC patients with AIDS-defining illness presented with AIDS-associated neurological disease, including cerebral toxoplasmosis and HIV-associated neurological disorder, whereas none were observed among PC patients. In both groups the death rate was low (3%, $n = 1/34$ for PC and 2%, $n = 1/41$ for DC); one patient died due to PJP and one died due to lymphoma.

The incidence of LD ($p = 0.020$), CD4 count < 350 cells/μL ($p = 0.037$) and < 200 cells /μL ($p = 0.022$) were statistically significantly associated with the ongoing COVID pandemic. Association with transmission risk was borderline significant ($p = 0.055$).

DISCUSSION

To our knowledge this is the first real-life cohort presenting novel data on the impact of COVID-19 in HIV late diagnosis in Germany.

Even with easy accessibility to testing facilities and the prompt treatment of newly diagnosed HIV patients, 40–55% of patients are still diagnosed with late diagnosis in Germany [5, 6]. Other European cohorts have shown similar LD rates between 42% and 58% [7–10]. In the COHERE cohort, being heterosexual, originating from southern Europe or being of African descent were found to be associated with the highest risk of LD [10]. Older age has also been associated with an increased risk of LD [5]. It is an urgent goal to diagnose HIV patients at an early stage as it is a known fact that LD leads to increased morbidity and mortality as well as increased health costs. The UNAIDS 95-95-95 goals are at increasing risk of being missed due to the ongoing focus on COVID-19 and the resulting missed opportunities of treating HIV patients. As reported in the UNAIDS HIV Services Tracking, a large, sustained decrease in HIV testing in the reporting countries was observed [11].

With the beginning of the COVID-19 pandemic in Germany in February 2020, we found the rate of LD to be rising at our infectious disease department. The overall rate of LD during the ongoing pandemic has shown a 40% increase over the pre-pandemic time-frame, resulting in a 3.4-fold higher odds ratio (95% confidence interval: 1.18–9.83). This is most likely due to the numerous impacts of the ongoing COVID-9 pandemic in Germany. Beginning with increasing numbers of SARS-CoV-2 infections in spring 2020, the fear of acquiring SARS-CoV-2 infection rose steadily, which led to an overall decreased consultation rate by, and access to, physicians. Therefore, possible symptoms of progressed HIV infection might have been neglected or their investigation postponed by the individual, or been misinterpreted due to the main focus on COVID-19.

Access to low-threshold testing was impeded by down-regulation of community service testing at checkpoints and municipal health centres. As a result, two main areas for detecting undiagnosed HIV infection (whether with symptoms or asymptomatic) were disrupted.

Concerning risk of transmission, we found a decreasing rate of new HIV infections in MSM which was also observed in an Italian cohort during the ongoing COVID-19 pandemic [12]. This could be due to reduced contacts during lockdown as well as the fewer possibilities for testing mentioned earlier, which is more widespread and implemented in this risk group. Previous cohorts have shown a decrease in late diagnosis in MSM over time, which might be due to the implementation of pre-exposure prophylaxis [10]. In our study we found an increase in LD among heterosexuals. Moreover, transmission via heterosexual contact has been described earlier as an associated risk factor for LD [11]. Indeed, this group

might be more affected by having less information about testing strategies as well as by a lack of awareness regarding their individual risk of infection and could therefore have been even more impeded during the ongoing COVID-19 pandemic.

Regarding the institution in which HIV infection was diagnosed, we found a shift towards diagnosis in hospital due to mandatory treatment, whereas diagnosis before COVID-19 was most often performed in specialist practices. However, due to the high rate of LD in our cohort, this finding has to be interpreted with caution. This reflects the fact that ongoing LD during the COVID-19 pandemic might be due to the reduced availability of low-threshold testing and reduced slots at general practitioners. Moreover, LD, with its concomitant laboratory and clinical abnormalities, requires special awareness, underlining the fact that all physicians, regardless of their speciality, need to be aware of HIV-associated symptoms and disease in order to determine the HIV diagnosis.

A low CD4 count reflects the impaired immune function and increased risk of developing AIDS-defining diseases, which all lead to increased morbidity and mortality. In our study, CD4 counts < 350 cells/μL and < 200 cells/μL were statistically significantly associated with the ongoing COVID-19 pandemic, underlining the fact that we need to put all our efforts towards diagnosing patients at an earlier stage in order to prevent severe immune dysfunction and subsequent AIDS-defining diseases.

At the same time, we found an almost doubled rate of AIDS-defining diseases during the ongoing COVID-19 pandemic. PJP, which is the most prevalent AIDS-defining disease, was found most often in our study. It is important to note that more than half of patients with PJP are so severely ill that they require intensive care treatment; 40% ($n = 2/5$) of DC patients with PJP who required intensive care treatment had to undergo mechanical ventilation via intubation, as compared with 25% ($n = 1/4$) of PC patients. The overall increased rate of AIDS-defining diseases raises morbidity and mortality, which also increases the cost of healthcare. Moreover, persistent organ damage or development of renal insufficiency after recovering from PJP or other AIDS-defining diseases has to be taken into consideration.

Interestingly, we diagnosed several patients with AIDS-related neurological disorders, whereas none had been observed in the comparable pre-COVID cohort. Since implementation of cART, incidence of HIV-associated neurological diseases has been decreasing, and thus patients with LD are still at an elevated risk [13]. In particular, AIDS-related neurological disorders cause significant and, most often, permanent harm to the patient and therefore early diagnosis is of vital importance. Both of our patients with cerebral toxoplasmosis still have tremendous neurological deficits. One patient who presented with hemiplegia due to cerebral toxoplasmosis and severely spread Kaposi sarcoma even went blind due to cytomegalovirus-associated retinitis.

Our study has several limitations. First, it is a monocentric study, and second it only reflects data from two time slots which are close together. The overall higher rate of LD might be overestimated due to coincidence and the historical fact of the increased amount of LD in our hospital, as it is well known for its special infectious disease department. Thus, this study reflects a real-life cohort being affected by the ongoing COVID-19 pandemic.

In conclusion we found an increased rate of LD in our cohort during the persisting COVID-19 pandemic despite stable annual numbers of new HIV diagnoses, which underlines the barriers to HIV testing as well as general care as a result of the focus on COVID-19. The outcome is more AIDS-defining diseases and higher hospitalization rates. Maintaining HIV testing opportunities and access to treatment during a pandemic is crucial if it is not to impede WHO elimination goals and we are to prevent an increase in AIDS-related morbidity and mortality.

AUTHOR CONTRIBUTIONS

KvB designed the study and concept. Sample collection was performed by all co-authors. Data analysis was performed by KvB. The manuscript was written by KvB and CB with full input from all co-authors.

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DATA AVAILABILITY STATEMENT

Data are available on request.

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