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ORIGINAL PAPER

Antiretroviral treatment indications and adherence to the German-Austrian treatment initiation guidelines in the German ClinSurv HIV Cohort between 1999 and 2016

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Abstract

Purpose The aim of the study was to assess guideline adherence to combined antiretroviral therapy (ART) in the German ClinSurv HIV Cohort and the real-life impact of the Strategic Timing of Antiretroviral Therapy (START) study, to identify patients not treated as recommended by new guidelines.

Methods We used data from the multicenter ClinSurv cohort of the Robert-Koch-Institute (RKI) between 1999 and 2016. Inclusion criteria were people living with HIV/AIDS, ≥ 18 years of age and cART naïve at the first visit (FV). Adherence was defined as starting cART within 6 months of crossing the $CD4^+$ T cell threshold as suggested by the German-Austrian treatment guidelines. Logistic regression was used to identify factors associated with non-adherence.

Results 11,817 patients met the inclusion criteria. We observed an overall adherence rate of 60%, in patients with treatment indication who started cART timely between 2002 and 2015. Adherence rate increased constantly, demonstrating a potential increase in patients, with treatment indication, starting cART within 6 months of presentation from 55% in 2008 to 94% in 2015. Patients reporting injection drug use (OR 2.18, 95% CI 1.70–2.95) and patients between 18 years and 39 years of age at the time of their first visit (OR 2.89, 95% CI 1.35–6.18) were identified as risk groups associated with non-adherence.

Conclusion The majority of patients below the $CD4^+$ T cell count threshold of applicable guidelines initiated treatment within 6 months. We observed a slowly diminishing proportion of patients not starting cART timely. Delayed treatment was more frequent in patients reporting injection drug use.

Keywords HIV · Antiretroviral therapy · START · Treatment guidelines · Adherence

Introduction

The HIV-AIDS epidemic has fundamentally changed by the introduction of highly active antiretroviral therapy (HAART) in the late 1990s [1, 2]. The initiation of HAART, or later called combined antiretroviral therapy (cART), has led to a substantial reduction of morbidity and mortality in People living with HIV/AIDS (PLWHA) [3]. Quality of life [4] and life expectancy has improved significantly during the past two decades [3, 5]. In 2016, approximately 36.7 million people were living with HIV [6]. As of October 2017, a 20.9 million people were accessing cART [6], compared to only 7.7 million in 2010 reflecting the global efforts to treat more patients to achieve the WHO/UNAIDS 90-90-90 targets by 2020 [7]. Ever since the introduction of cART, there has been an ongoing discussion on the optimal timing

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to initiate therapy due to uncertainty about risks and benefits. Adverse drug reactions [8], known side effects of some antiretroviral remedies [9], long-term toxicity [10], the prevalence of drug resistance mutations [11] have to be weighed against individual health benefits and declining rates of HIV transmission [12]. Further, public health aspects of cART have become more important due to the advancements in treatment, implementation of lifelong therapies and, therefore, increasing economic burden [13–15].

Very recently, the huge landmark trial, Strategic Timing of Antiretroviral Therapy (START) has demonstrated strong positive effects by starting cART immediately after diagnosis of HIV infection irrespective of the $CD4^+$ T cell count. It seems that a longstanding scientific debate about the ideal timing of starting cART might have ended [16]. The results of the START-trial [16] as well as the TEMPRANO-trial, that showed similar results [17] are reflected in actual international guidelines in Europe, Great Britain and the US [18–20]. Consequently, the US-guidelines now recommend treating any HIV-infected patient with cART, regardless of his or her $CD4^+$ T cell count at first visit (FV) [18]. In the past, the German-Austrian HIV treatment guidelines used to recommend cART initiation at lower $CD4^+$ T cell count thresholds in HIV-infected individuals. The current German-Austrian guidelines are adapted at international guidelines in order to start cART immediately at FV irrespective of $CD4^+$ T cell count [21–24].

Little data exist about the adherence to the treatment guidelines by physicians that treat HIV-infected individuals. This analysis aims to assess guideline adherence in Germany as found in the German ClinSurv HIV Cohort. Further, we aimed to assess the real-life impact of the START study on treatment of HIV-infected patients in Germany. The results of this study will serve as a basis for further discussion concerning cART guidelines and the importance for patients, physicians, public health and costs for the German health care system.

Methods

ClinSurv data

We performed a retrospective subgroup analysis using data from the German Clinical Surveillance of HIV Disease cohort of the Robert Koch Institute (RKI). The clinical surveillance of HIV, ClinSurv HIV is a long-term observational multi center, prospective cohort study of HIV positive patients (since 1999). The aim of this cohort study is to analyze antiretroviral treatment outcome and success over time as well as the development of AIDS-related diagnoses and death in patients with chronic HIV infection. The cohort acts as an enlargement of the national HIV surveillance in the clinical HIV care setting. The details of the ClinSurv HIV cohort have been published elsewhere [25]. Data for this analysis were collected from 14 university hospitals and specialized HIV treatment centers. Subjects meeting the following criteria were considered for our analysis: PLWHA of the ClinSurv cohort, starting cART between 1999 and June 2016, ≥ 18 years. We excluded patients who were not treatment naïve at the time of the FV, patients without baseline data (including $CD4^+$ T cell count and VL) 3 months prior to starting cART and patients who received initial therapy before 1999 (Fig. 1).

Statistical analysis

Patient characteristics at the time of their FV and the initiation of cART were displayed as absolute numbers plus percentages, medians plus interquartile ranges (IQR) or means plus 95% confidence intervals (95% CI), as appropriate. Parametric and non-parametric tests were used for normally and not-normally distributed data. VL measurements were either reported as an integer or as a measurement below the limit of quantification (<50, <500, <1000). Therefore, the half of the limit of detection was used in 155 cases [26].

We assessed adherence according to changing treatment guidelines by defining adherence as initiating cART within 6 months of crossing the $CD4^+$ T cell count threshold recommended by the applicable German-Austrian cART guidelines for each year from 2002 to 2016, categorized in recommended, consider/offer and not recommended [22, 23, 27, 28] (Supplementary Table 1). We further performed

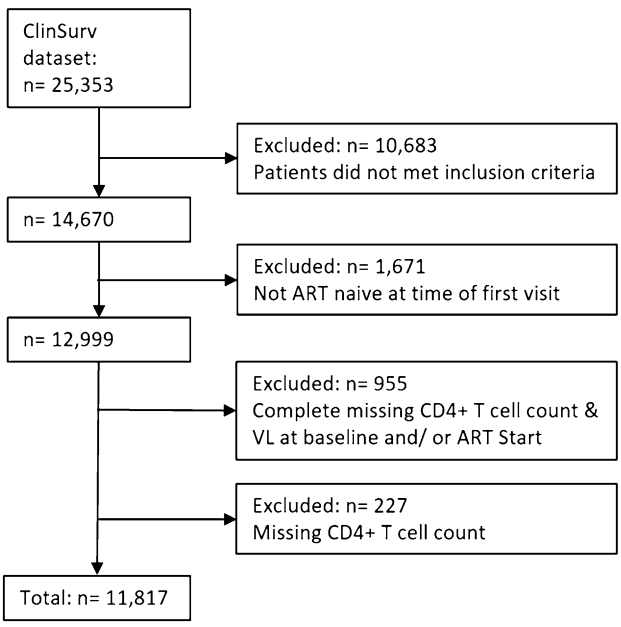

Fig. 1 Flow chart of selected cases due to predefined inclusion and exclusion criteria

two uni- and multivariable logistic regression models, using backward elimination to identify variables that are associated with the outcome variable. Odds ratio (OR) and 95% CI were used to report the direction and strength of association.

Time-to-event parameters were estimated using Kaplan–Meier method. The primary outcome was the initiation of cART, whereas the time to event was calculated as the time from date of the FV followed until the initiation of cART. Differences between groups were analyzed and compared using the log rank test. Pairwise log rank comparisons were used to determine differences in time to event within each group. To counter multiple comparisons, we applied a Bonferroni correction [29]. We further used a Cox regression model to estimate the proportional hazard and 95% CI to display the direction and strength of the association between variables of interest, with the number of months from the FV until the initiation of cART as time scale.

Based on exploratory analysis, we categorized VL, $CD4^+$ T cell count, age and the year of the FV. VL categories were defined as follows: < 10,000, 10,000–99,999, ≥ 100,000. $CD4^+$ T cell categories as < 200, 200–349, 350–499 and ≥ 500. Age groups 18–39, 40–69 and ≥ 70. Year of FV: before 2002, 2002–2007, 2008–2014 and 2015–2016. Symptomatic-HIV disease stages, including diagnosis reported within 1 month before the FV, were categorized based on the disease classification System of the Center for disease control and prevention (CDC). Self- reported HIV risk behavior were categorized in men having sex with men (MSM), people with injection drug use (PWID), heterosexuals (HTS), people from an endemic area (countries with a HIV prevalence > 1%), and others (including infected people due to prenatal and perinatal infection, blood transfusion and blood product and people with hemophilia (PwH) and unknown. Analyses were accomplished by using Stata (Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Results

Study population

Data on 25,353 patients enrolled in the ClinSurv cohort between 1999 and June 2016 were available. Our final analysis was performed on 11,817 patients who met the inclusion criteria (Fig. 1). Patient characteristics, demographic and clinical data are shown in Table 1. The patient population was predominantly male (79.3%, $n = 9373$) from a European country (80.6%, $n = 9520$) with a median age of 37 years (IQR 30–45), at time of the FV. The greatest amount of patients started treatment within 6 months (65%), followed by 12 (7%) and 18 (5%) months after first presentation. The median VL and $CD4^+$ T cell count at the time of the FV was 66,069 copies/ml (IQR 15,500–233,000) and 275 cells/mm^3 (IQR 109–455), compared to 88,550 copies/ml (IQR 25,119–277,042) and 188 cells/mm^3 (IQR 86–331) at the start of cART. The initial cART regime contained 39.9% (4711) NRTI/PI/boost, 36.2% (4282) NRTI/NNRTI and 8.7% (1,029) NRTI/II. A total of 1063 (9.0%) and 1008 (8.5%) patients were symptomatic according to CDC category B and C, respectively 1 month before and at the time of the FV [30]. Overall, 639 (5.5%) deaths have been reported between 1999 and June 2016.

Adherence to treatment initiation guidelines

Adherence to the German-Austrian cART initiation guidelines is displayed in Fig. 2, comparing patients with and without treatment indication to start cART regarding $CD4^+$ T cell count based on the applicable treatment initiation guidelines from 2002 until 2015 [21–24, 27, 28].

We observed an overall adherence rate of 59.7%, in patients with treatment indication who started cART timely between 2002 and 2015. Since 2008, the amount of patients who started cART within 6 months increased constantly from 53 to 75% in 2014. In 2015, more than 94% of all patients initiated cART as recommended within 6 months after their FV. Simultaneously, the overall proportion of patients with treatment indication who did not start therapy though recommended declined from 25% in 2002 to 8% in 2014.

Non-adherence to treatment initiation guidelines

To identify factors that are possibly associated with non-adherence, we conducted two univariate and multivariable logistic regression models. In the first model, we analyzed non-adherence to treatment guidelines in patients without treatment indication who initiated cART within 6 months after their FV (Supplementary Table 2). In the second model, we examined non-adherence in patients with treatment indication who did not initiate cART within 6 months after the FV (Table 2). We identified clinical and geographical characteristics summarized in Supplementary Table 2 and Table 2. Following key findings were identified in the multivariable analyses.

Patients with their first visit in 2002–2007 and 2008–2014 were significantly associated with a delayed initiation of cART (OR 9.66, 95% CI 6.11–15.26 and OR 5.08, 95% CI 3.21–8.03) (vs first visit in 2015–2016), as well as patients between 18 and 39 years of age at the time of their first visit (OR 2.89, 95% CI 1.35–6.18). Delay in treatment initiation was significantly more likely in patients reporting injection drug use (OR 2.18, 95% CI 1.70–2.95) and patients with a clinical disease stage A&B (OR 1.76, 95% CI 1.21–2.57) (Table 2). Moreover, female patients and patients from Asia, Australia ore New Zealand were significantly more likely to

Table 1 Characteristics at the time of the first visit (FV) of 11,817 patients included in the subgroup analysis of the ClinSurv cohort

Patient characteristics	No of patients ($n = 11,817$)	(%)
Gender		
Female	2444	20.7
Male	9373	79.3
Risk group*		
MSM	5935	50.2
PWID	770	6.5
HTS	1939	16.4
Endemic area	1620	13.7
Other	1553	13.1
Country of origin		
Europe	9520	80.6
North-Eastern Africa	96	0.8
Sub-Saharan Africa	1367	11.6
Asia, Australia and New Zealand	391	3.3
North and Latin-American	245	2.1
Missing	198	1.7
$CD4^+$ T cell count at FV	Median: 275	IQR: 109–455
< 200	4514	38.2
200–349	2700	22.8
350–499	2200	18.6
≥ 500	2403	20.3
Viral load (copies/µl)	Median: 66,069	IQR: 15,500 – 233,000
< 10,000	2249	19.0
10,000–99,999	4352	36.8
≥ 100,000	4680	39.6
Missing	536	4.5
Age (groups)	Median: 37	IQR: 30–45
18–39	2796	23.7
40–69	8410	71.2
≥ 70	611	5.2
Year of FV	Median: 2007	IQR: 2002–2011
< 2001	2266	19.2
2002–2007	4285	36.3
2008–2014	4.824	40.8
2015–2016	442	3.7
Therapy initiation after FV (months)	Median 1	IQR: 0–15
< 6	7657	64.8
6–11	791	6.7
12–17	577	4.9
18–24	437	3.7
≥ 24	2,355	19.9
CDC category at FV**		
A	38	0.3
B	1063	9.0
C	1008	8.5
No diagnosis or missing	9708	82.2
cART regime		
NRTI/PI/boost	4711	39.9
NRTI/NNRTI	4282	36.2
NRTI/II	1029	8.7
NRTI	461	3.9

Table 1 (continued)

Patient characteristics	No of patients ($n = 11{,}817$)	(%)
NRTI/II/boost	294	2.5
Others	1040	8.8

*MSM, men who have sex with men; HTS, heterosexual; PWID, persons who inject drugs; endemic area, people from countries with a HIV prevalence > 1%; others, including infected people due to prenatal and perinatal infection, blood transfusion and blood product and people with hemophilia (PwH) and unknown

**The HIV disease classification (Center for Disease Control and Prevention (CDC) categories A, B and C) including diagnosis reported within 1 month before the First Visit (FV)

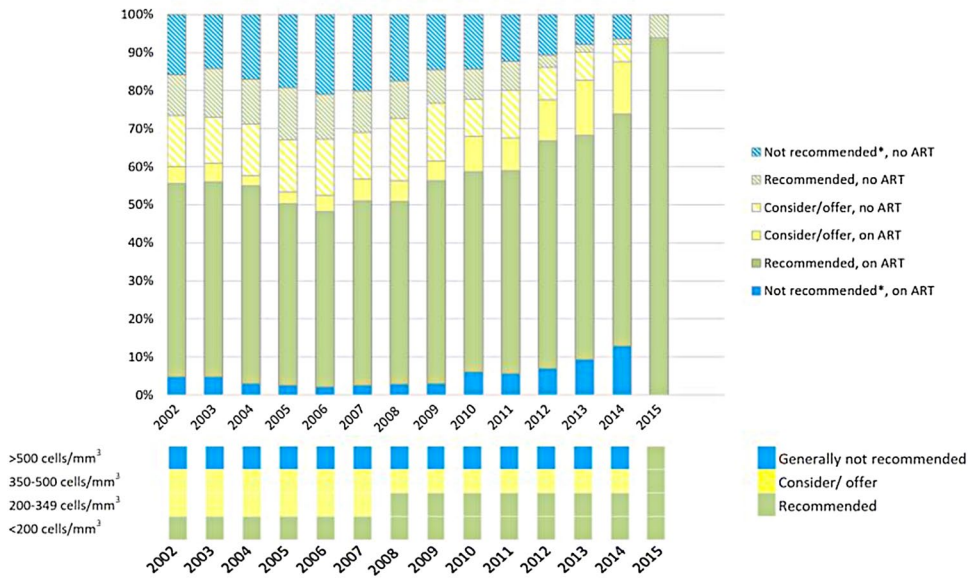

Fig. 2 Adherence to the German-Austrian cART guidelines applicable for each year, considering patients with treatment indication due to the CD4$^+$ T cell count thresholds (including additional therapy recommendations such as CDC stage C, > 50 years of age, viral load > 100,000 and without treatment indication who initiated cART within the first 6 months after the first visit (FV). *Not recommended, but acceptable according to experts' opinion

initiate therapy even though the guidelines recommended otherwise (OR 1.65, 95% CI 1.07–2.57 and OR 2.78, 95% CI 1.05–7.38, respectively) (Supplementary Table 2).

Time to initiate cART

Time to event analysis indicated strong prognostic factors regarding the time to initiate cART within 6 months. We observed significant associations with an earlier start of cART after FV regarding lower CD4$^+$ T cell counts ($p < 0.001$), higher VL ($p < 0.001$), older age ($p < 0.001$), the HIV disease stages ($p < 0.001$) a more current FV in the period of < 2001–2015 ($p < 0.001$), region of origin ($p < 0.001$) and reported risk groups ($p < 0.001$). Pairwise comparison revealed significant differences among subgroups for early initiation of cART (Supplementary Table 3). We further calculated a multivariable Cox regression model using backward elimination to identify associating factors to start cART. The adjusted Hazard Ratios (HR) for the association of factors at baseline with causes to start cART are presented in (Table 3). Patients with a higher baseline CD4$^+$ T cell count were significantly less likely to start cART compared to patients with a CD4$^+$ T cell count < 200 (CD4$^+$ T cell count ≥ 500 HR 0.37; 95% CI 0.30 − 0.45; 350–499 HR 0.25; 95% CI 0.19 − 0.31; 200–349 HR 0.57; 95% CI 0.49–0.66). Patients with their FV in the time period from 2008 to 2014 and 2015–2016 were significantly more likely to initiate cART compared to patients with their first visit before 2001 (HR 1.29; 95% CI 1.14–1.82 and HR 1.44; 95% CI 1.14–1.82, respectively). Same trends were observed in patients with a symptomatic HIV disease condition (CDC category C) at the time of the FV (HR 1.08; 95% CI 0.98–1.18).

Discussion

The main goal of our study was to evaluate adherence to treatment guidelines in Germany over a 17-year period with multiple shifts in recommended thresholds for treatment initiation. To that end, we retrospectively analyzed data of the ClinSurv cohort, including epidemiological and medical data from 11,817 PLWHA, treated in 14 major HIV treatment centers and university hospitals throughout Germany. To our knowledge, this is the first study focusing on treatment routines in the context of contemporary guidelines of German clinicians.

Table 2 Univariate and multivariable logistic regression model for non-adherence [patients with treatment indication who did not start therapy within 6 months after the first visit (FV)] displayed with OR and 95% CI, adjusted for gender, region of origin, year of FV, HIV disease classification (Center for Disease Control and Prevention (CDC) categories A, B & C) at FV ($n = 7964$)

	Univariate analysis		Multivariable analysis**	
	OR (95% CI)	*p* value*	OR (95% CI)	*p* value*
Total				
FV year				
2002–2007	9.07 (5.81–14.17)	**< 0.001**	9.66 (6.11–15.26)	**< 0.001**
2008–2014	4.88 (3.13–7.64)	**< 0.001**	5.08 (3.21–8.03)	**< 0.001**
2015–2016				
Gender				
Male				
Female	0.80 (0.71–0.91)	**< 0.001**		
Risk				
HTS				
MSM	1.15 (1.01–1.32)	**0.025**	1.12 (0.75–1.67)	0.566
PWID	1.44 (1.15–1.80)	**0.001**	2.18 (1.70–2.95)	**0.013**
ENDEMIC*	0.64 (0.53–0.76)	**< 0.001**	0.60 (0.16–2.31)	0.466
Others/unknown	0.69 (0.58–0.83)	**< 0.001**	0.66 (0.37–1.17)	0.160
Age (groups)				
18–39	1.39 (1.12–1.71)	**0.002**	2.89 (1.35–6.18)	**0.006**
40–69	1.10 (0.99–1.34)	0.329	1.40 (0.73–2.69)	0.306
≥ 70				
Region of origin				
Europe				
North-East Africa	0.52 (0.29-0-93)	**0.028**		
Sub-Saharan Africa	0.60 (1.51–1.71)	**< 0.001**		
Asia, Australia and New Zealand	0.54 (0.40–0.72)	**< 0.001**		
North and Latin America	0.87 (0.63–1.21)	0.416		
CDC category				
A&B	1.69 (1.22–2.36)	**0.002**	1.76 (1.21–2.57)	**0.003**
C				

*p values (< 0.05) in bold depict significant results

**Multivariable model adjusted for gender, region of origin, and CDC category

We found that the majority of patients below the $CD4^+$ T cell count threshold of applicable guidelines from 2002 to 2016 [22, 23, 27, 28] received treatment within 6 months of presentation. Our analysis revealed that adherence increased constantly since 2008 from 55% to 94% in 2015. This finding might reflect that patients' willingness to adhere to the recent guidelines increased and that patients reached a conscious awareness that therapy guidelines are desired and beneficial. In addition, the introduction of more durable and patient-friendly drugs classes, i.e. integrase inhibitors or next generation protease inhibitors, may have improved adherence to treatment guidelines among patients and clinicians. Our results correspond to the results of Schmidt et al. [31], who observed an increase in PLWHA receiving cART in Germany from 2006 to 2013. Moreover, the results show that the amount of patients on cART increased by 6% from 2014 to 2015, which is a more pronounced increase compared to previous years (Fig. 2). We hypothesize that especially the newly presenting patients were affected by the preliminary- [32, 33] and final results of the START trial [16], resulting in an update of treatment guidelines in 2015 [21].

Although, our analyses revealed that adherence to treatment initiation guidelines increased over time, we identified risk groups with suboptimal adherence to treatment initiation guidelines. PWID and people with younger age did not start therapy timely despite treatment indication. These findings are possibly linked to the results of our previous study, which elucidated that the risk group of PWID represent a source of onward DRM transmission among therapy naïve individuals in the Cologne-Bonn region in Germany highlighting the need to implement prevention interventions targeting the risk group of PWID [34]. Similar trends, demonstrating that injection drug use negatively affects adherence and testing behavior, have already been observed in previous studies [35, 36]. Anticipated stigma, a low socioeconomic status and poor access to medical care can also negatively affect testing behavior and treatment adherence

Table 3 Cox regression model. Hazard ratios (HRs) and 95% confidence intervals (CI) associated with starting cART from cox model adjusted for gender, country of origin, HIV disease classification (Center for Disease Control and Prevention (CDC) categories A, B & C) at time of the First Visit (FV), year of FV, CD4 cell count and VL at FV ($n = 11,817$)

	HR (95% CI)	*p* value*
Total		
Gender		
Female		
Male	1.06 (0.94–1.16)	0.290
VL FV		
< 10,000		
10,000–99,999	0.94 (0.80–1.10)	0.420
≥ 100,000	1.02 (0.88–1.17)	0.835
$CD4^+$ T cell count (cells/µl) at FV		
< 200		
200–349	0.57 (0.49–0.66)	**< 0.001**
350–499	0.25 (0.19–0.31)	**< 0.001**
≥ 500	0.37 (0.30–0.45)	**< 0.001**
FV year		
< 2001		
2002–2007	1.02 (0.90–1.15)	0.420
2008–2014	1.29 (1.14–1.82)	**< 0.001**
2015–2016	1.44 (1.14–1.82)	**0.002**
CDC category at FV		
A&B		
C	1.08 (0.98–1.18)	0.092

*p values (< 0.05) in bold depict significant results

[37]. In Addition, we identified that female patients were significantly more likely to initiate therapy even though the guidelines recommended otherwise. This might be associated with the amount of pregnant women or women of childbearing age, which could not have been taken into account in our analysis. Factors most strongly associated with the initiation of cART in the Cox regression model were the year of the FV and the $CD4^+$ T cell count, reflecting adherence to the applicable treatment guidelines (Table 3).

Our study has limitations based on the used methodology and data source. We identified inconsistencies regarding the documentation of the VL and $CD4^+$ T cell count. Values were either recorded directly or as a measurement below the limit of quantification (< 50, < 500). To get consistent results, we used the half of the limit of detection in 155 cases for our analysis, a common method used in prior studies [26]. Our results might be biased, as it is less likely that individuals from hard to reach populations were included in our dataset. Among these populations, the initiation of care, the overall use of cART and the attitude towards starting cART are less frequent [38]. Thus, HIV infections of these populations cannot be reported. However, our study population was comparable with the population of HIV PLWHA in Germany [39] as the ClinSurv cohort capture a fairly representative sample population of HIV patients in care [40]. The data of the ClinSurv cohort was not fully captured for 2015–2016; consequently data from 2015 to 2016 are comparable to a limited extent only and need to be interpreted with caution.

In conclusion, we found evidence that adherence to treatment initiation guidelines increased constantly since 2008. The majority of patients below the $CD4^+$ T cell count of applicable guidelines received treatment within 6 months of presentation and the number of patients initiating cART, despite the $CD4^+$ T cell count thresholds of applicable cART guidelines, increased significantly. There was a slowly diminishing proportion of patients not starting cART timely, despite a $CD4^+$ T cell count under the recommended threshold. PWID were identified as risk groups associated with non-adherence, which support the need to improve access to treatment especially among the risk group of PWID. Further analyses must aim at identifying barriers and reasons for not starting treatment to educate measures towards increasing the share of patients with timely treatment initiation.

Our study has demonstrated customary treatment strategies by HIV practitioners in Germany in the context of developing evidence and guidelines and addresses perspectives for the future development of cART strategies and the progress towards the UNAIDS 90-90-90 [7]. We established that changes of treatment guidelines led to a substantial increase of patients receiving cART. In the future, it will be important to develop effective interventions towards better coverage of vulnerable patient groups such as PWID by guidelines and individual therapeutic considerations.

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Author contributions JV and MS designed the study, analyzed and interpreted the data. MS drafted the primary draft of the manuscript. BG, CK and DS provided data, and contributed critically important ideas on how to interpret the data. PS, BG, CK, DS, MP, CL and GF revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest This study is a project within the TP-HIV by the German Centre for Infection Research (DZIF) (NCT02149004). We declare that all authors have no conflicts of interest.

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