Antiretroviral Treatment Indications and Guideline Adherence in the German ClinSurv HIV Cohort between 1999-2014: Projecting the Impact of the START Trial in Germany

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Background

➢ Ever since the invention of Antiretroviral Therapy (ART), there has been an ongoing discussion on the optimal timing to initiate therapy due to uncertainty about risks and benefits.
➢ It has been general practice to start ART above a certain CD4 threshold level. Recommendation for this level has changed over time.
➢ Little data exist about the exact treatment strategies and drug combinations of HIV specialists used in clinical practice in Germany.
➢ Adherence to ART guidelines is <100% due to medical reasons and/or individual choices of patients and physicians.
➢ Our analysis aims to predict the real-life impact of the Strategic Timing of Antiretroviral Therapy (START) study and to identify a proportion not benefitting from improved guidelines.

Methods

➢ We used data from the prospective multicenter German Clinical Surveillance of HIV Disease (ClinSurv) cohort of the Robert-Koch-Institut (RKI).
➢ Inclusion criteria were HIV positive, age >18 years, and ART naïve at the first visit.
➢ Time-to-event parameters were estimated using Kaplan-Meyer method. Differences between groups were analysed and compared using the log rank test.
➢ Pairwise log rank comparisons were conducted to determine differences in time to event within each group.
➢ Bonferroni correction was applied to counter multiple comparisons.
➢ Factors associated with initiation of ART were assessed by cox regression methods.
➢ Guideline adherence was defined as starting ART within six months of crossing the CD4 threshold suggested by current German-Austrian HIV treatment guidelines (Fig. 4).

Results

Participants:
Of 25,353 patients enrolled in the ClinSurv HIV cohort between 1999 and June 2016, 11,817 patients met the inclusion criteria (Table 1). Patients were largely males (79.3%) from European countries (80.5%) aged 37 years (median; IQR 30-45). The median viral load (VL) and CD4 cell count at first visit was 66,069 copies/ml and 275 cells/mm³, compared to 88,550 copies/ml and 188 cells/mm³ at the start of ART. Patients started treatment within six (64.8%), 12 (6.7%) and 18 (4.9%) months after first presentation. Preferred ART regimens were NRTI/PI/boost and NRTI/NNRTI (39.9%, n=4,711 and 36.2%, n=4,282).

Table 1: Characteristics of 11,817 patients included in the subgroup analysis of the ClinSurv cohort. Median time to initiate ART (month and baseline characteristics (Kaplan-Meyer method) with overall comparison using Log-rank test.

	No of patients (n = 11,817)	(%)	Median time (months) to start ART (95%CI)	Overall comparison p-value*
Sex				0.032
Female	2,444	20.7	1 (0.7, 1.2)	
Male	9,373	79.3	1 (0.8, 1.1)	
Risk group				<0.001
MSM	5,935	50.2	2 (1.7, 2.2)	
PWID	770	6.5	4 (2.0, 5.9)	
HSX	1,939	16.4	1 (0.7, 1.2)	
Endemic area	1,620	13.7	1 (0.5, 1.1)	
Other**	1,553	13.2	1 (0.7, 2.2)	
Country of origin				<0.001
Europe	9,520	80.6	1 (0.8, 1.1)	
Africa	1,463	12.4	1 (0.3, 4.5)	
Asia, Australia & New Zealand	391	3.3	1 (0.2, 3.1)	
North & South America	245	2.1	2 (1.1, 2.8)	
CD4 count/µl at first visit	Median: 275	IQR: 109-455		<0.001
<200	4,514	38.2	0 (0, 1.0)	
200 - 349	2,700	22.8	2 (1.8, 2.1)	
350 - 499	2,200	18.6	10 (8.9, 11.0)	
>500	2,403	20.3	25 (23.0, 26.9)	
HIV-1 RNA (copies/µl) at first visit	Median: 66,069	IQR: 15,500-233,000		<0.001
0 - 9,999	2,249	19.0	7 (5.2, 8.7)	
10,000 - 99,999	4,352	36.8	3 (2.6, 3.3)	
>100,000	4,068	34.4	0 (0, 1)	
> 1mio.	612	5.2	0 (0, 1)	
Age (years)	Median: 37	IQR: 30-45		<0.001
18-39	1,903	21.1	2 (1, 2.2)	
40-69	5,645	62.7	1 (0.8,1.2)	
≥70	1,461	16.2	0 (0, 4.2)	
Year of first visit	Median: 2007	IQR: 2002-2011		<0.001
1995-1999	1,631	13.8	3 (2.1, 3.8)	
2000-2004	3,456	29.2	2 (1.7, 2.2)	**
2005-2009	3,737	31.6	2 (1.6, 2.3)	
2010-2014	2,551	21.6	0 (0.2, 1.3)	
2015-today	442	3.7	0 (0.2, 1.1)	

*Log-rank overall comparison (p<0.05)
**Including infected people due to prenatal and perinatal infection, blood transfusion and blood product and people with haemophilia (PwH)

Time to event analysis:
Statistically significant differences in time to initiate ART were observed regarding CD4 cell count level (p<0.001) and VL at the first visit (p<0.001), HIV disease stage (<0.001) age (p<0.001), gender (p<0.032), year of the first visit (FV) (p<0.001), HIV associated diseases (p<0.001), country of origin (<0.001) and risk group (<0.001) (Figure 1).

Cox regression:
➢ Variables with (p< 0.2) in the bivariate analysis or potential confounders were included in our final model.
➢ The adjusted Hazard Ratios (HR) towards starting ART indicating, a lower CD4 cell count, a higher viral load and year of first visit 2010-2014 compared to before 2000 were significantly associated with higher rates of ART initiation (Figure 2).

	HR (95%CI)
Age (years)	1.004 (1.003-1.006)
Year of first visit (ref. bef. 2000) 2010-2014	2.08 (1.90-2.28)
2005-2009	1.34 (1.23-1.46)
2000-2004	1.06 (0.98-1.16)
CD4 value at first visit (ref.>500) <500	1.40 (1.31-1.50)
<350	2.43 (2.27-2.61)
<200	5.33 (4.96-5.73)
HIV-1 RNA at first visit (ref. >0-9,999) >1 mio.	1.28 (1.20-1.36)
>100,000	1.52 (1.42-1.62)
>10,000	1.52 (1.37-1.69)

Figure 2: Hazard ratios (HRs) and 95% confidence intervals (CI) associated with starting ART from the final cox model adjusted for gender, country of origin, year of first visit, CD4 cell count and VL at the time of the first visit.

Adherence to treatment guidelines
➢ The overall adherence rate to ART treatment guidelines based on CD4 threshold (Figure 4) was relatively high between 2002 and 2015 and increased constantly from 2008 until 2015 (Figure 3).
➢ Indicating a potential increase in patients, with treatment indication, starting ART within 6 months of presentation, from 56% in 2008 to 93% in 2015.
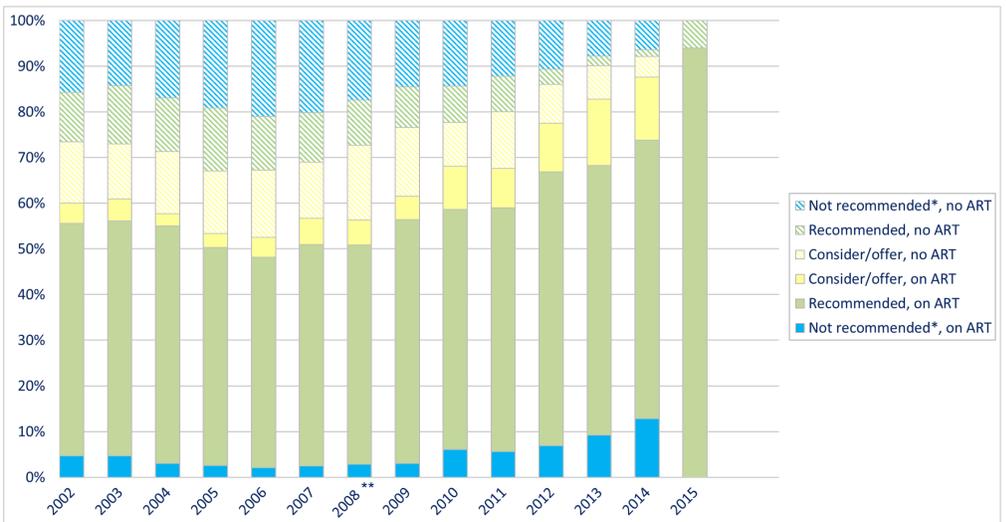
Figure 3: Adherence to the German-Austrian ART guidelines applicable for each year, considering patients with treatment indication due to the CD4 cell count and CDC-B or C stage and without treatment indication who initiated ART within the first six months after the first visit. *Not recommended, but acceptable according to experts opinion. ** Modifications to the guidelines in September 2008 were taken into account from 2009.
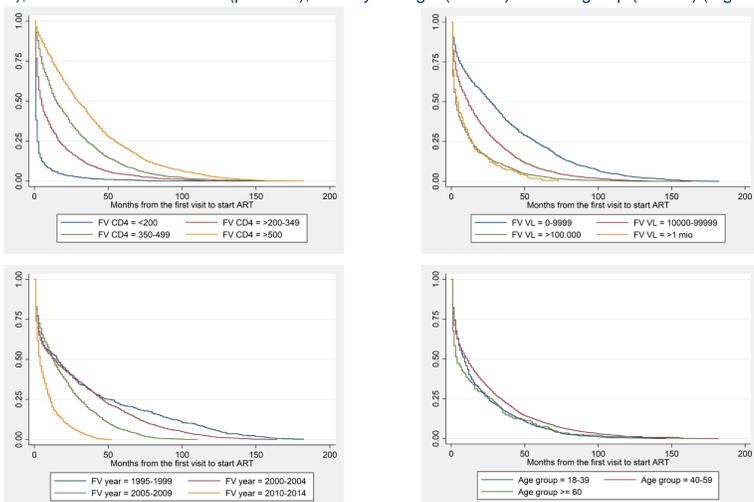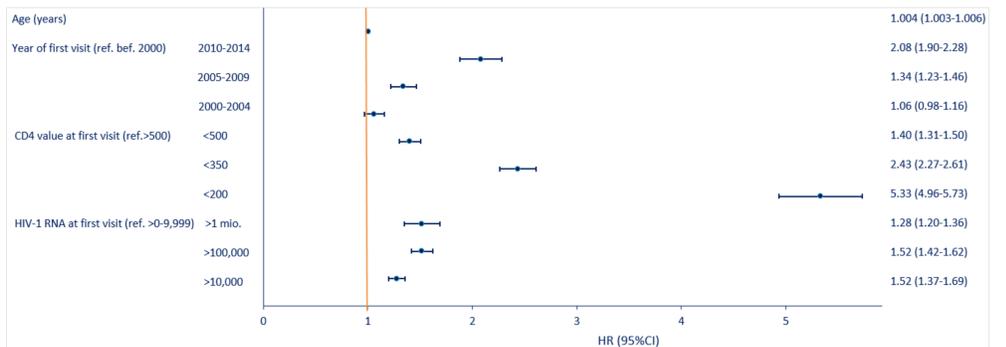
Figure 1: Unadjusted cumulative proportion of ART initiation by VL, CD4 cell count and age at time of the first visit and the year of the first visit.

CD4+ count thresholds of the German-Austrian HIV treatment guidelines

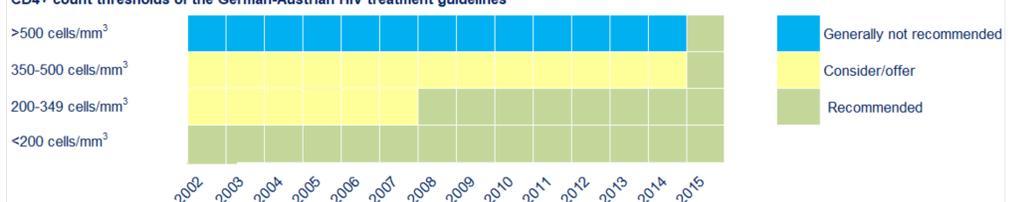Legend: Generally not recommended; Consider/offer; Recommended

Figure 4: Evolution of CD4+ count criteria for starting ART in asymptomatic HIV infected individuals, according to the German-Austrian HIV treatment guidelines (2002-2012).

Conclusion

The majority of patients below the CD4 threshold of applicable guidelines received treatment within six months of presentation. Based on our observation we can state, that a considerable share of newly presenting patients was affected by results of the START trial in 2015. However, we observed a slowly diminishing proportion of patients not starting ART timely, despite a CD4 count under the recommended threshold.

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