

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

M. Stecher^{1,3}, D. Schmidt², C. Kollan², B. Günsenheimer-Bartmeyer², C. Lehmann^{1,3}, G. Fätkenheuer^{1,3}, J.J. Vehreschild^{1,3}, on behalf of the ClinSurv Study Group

¹University Hospital of Cologne, Cologne, Germany, ²Robert-Koch-Institute, Berlin, ³Germany German Center for Infection Research (DZIF), partner site Bonn-Cologne, Cologne, Germany

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.

Results

Participants:

Of 23,181 patients enrolled in the ClinSurv HIV cohort between 1999 and December 2014, 9,009 patients met the inclusion criteria (Table 1). Patients were largely males (78.5%) from European countries (79.9%) aged 48 years (median; IQR 41-55). The median viral load (VL) and CD4 cell count at first visit was 73,470 copies/ml and 250 cells/mm³, compared to 91,454 copies/ml and 204 cells/mm³ at the start of ART. Patients started treatment within six (67%), 12 (7%) and 18 (5%) months after first presentation. Preferred ART regimens were NRTI/PI/boost and NRTI/NNRTI (42.2%, n=3,802 and 38.6%, n=3,479).

Table 1: Characteristics of 9,009 patients included in the subgroup analysis of the ClinSurv cohort. Median time to initiate ART (month and baseline characteristics (Kaplan-Meier method) with overall comparison using Log-rank test.

	No of patients (n = 9,009)	(%)	Median time (months) to start ART (IQR)	Overall comparison p-value*
Sex				0.032
Female	1,934	21.5	5 (1, 15.5)	
Male	7,075	78.5	4 (1, 17)	
Risk group				<0.001
MSM	4457	49.5	5.5 (1, 15.5)	
PWID	550	6.1	9 (1.5, 21.5)	
HSX	1471	16.3	5 (1, 16.5)	
Endemic area	1326	14.7	2 (0.5, 12)	
Other	24	0.3	11.5 (2, 31.5)	
Country of origin				<0.001
Europe	7,198	79.9	5.5 (1, 16)	
Africa	1,176	13.1	2.5 (0.5, 13.5)	
Asia, Australia & New Zealand	320	3.6	2 (0.5, 8)	
North & South America	263	2.0	4.5 (1, 15.5)	
CD4 count/μl at first visit	Median: 250	IQR: 93-426		<0.001
<200	3,740	41.5	0.5 (0.5, 1)	
200 - 349	2,078	23.1	2.5 (1, 8.5)	
350 - 499	1,597	17.7	7.5 (2.5, 18)	
>500	1,594	17.7	14.5 (6, 27.5)	
HIV-1 RNA (copies/μl) at first visit	Median: 73.470	IQR: 18.000-256.027		<0.001
0 - 9,999	1,659	18.4	13.5 (3, 28.5)	
10,000 - 99,999	3,414	37.9	6 (1.5, 15.5)	
>100,000	3,430	38.1	1.5 (0.5, 7)	
> 1mio.	506	5.6	2 (0.5, 7)	
Age (years)	Median: 48	IQR: 41-55		<0.001
18-39	1,903	21.1	4.5 (1, 13)	
40-59	5,645	62.7	5.5 (1, 17)	
≥60	1,461	16.2	2 (0.5, 13)	
Year of first visit	Median: 2006	IQR: 2002-2010		<0.001
1995-1999	695	7.7	8 (1, 25.5)	
2000-2004	2,875	31.9	7 (1, 23)	
2005-2009	3,149	35	6.5 (1.5, 15.5)	
2010-2014	2,290	25.4	2 (0.5, 5.5)	

*Log-rank overall comparison (p<0.05)

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).

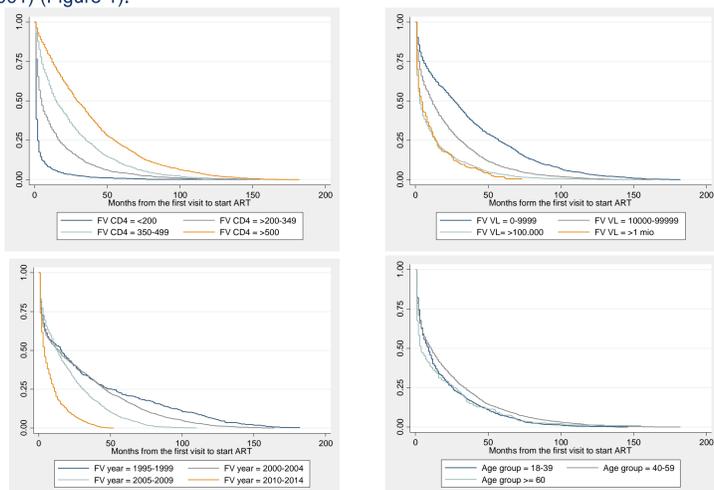


Figure 1: Unadjusted cumulative proportion of ART initiation by VL, CD4 cell count and age at time of the first visit and the year of the first visit.

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-Meier 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).

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 and year of first visit 2010-2014 compared to before 2000 were significantly associated with higher rates of ART initiation (Figure 2).

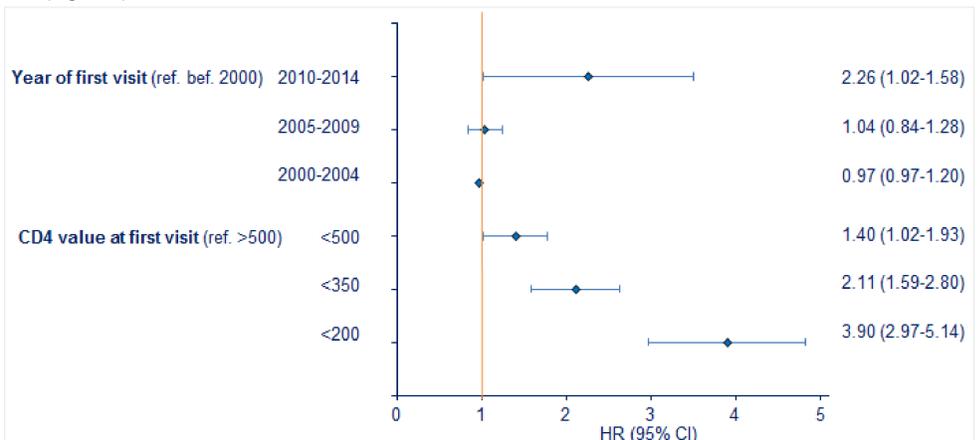


Figure 2: Hazard ratios (HRs) and 95% confidence intervals (CI) associated with starting ART from the final cox model adjusted for gender, country of origin, year of first visit, CD4 cell count and VL at the time of the first visit.

Adherence to treatment guidelines

- The overall adherence rate to ART treatment guidelines based on CD4 threshold (Figure 4) was relatively high between 2002 and 2013 and increased constantly from 2008 (Figure 3).
- Indicating a potential increase in patients starting ART within 6 months of presentation, from 53% in 2002 to 85% in 2013.

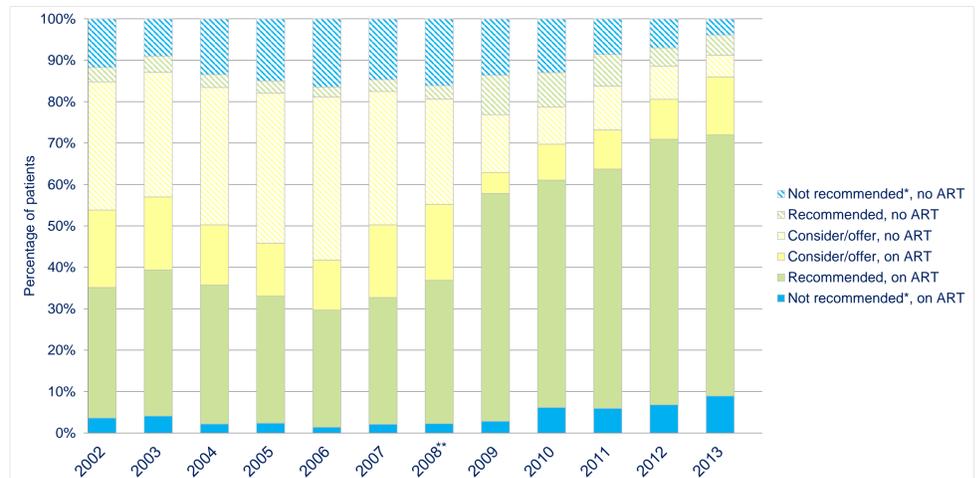


Figure 3: Adherence to the German-Austrian ART guidelines applicable for each year, considering patients with treatment indication due to the CD4 cell count and CDC-B or C stage and without treatment indication who initiated ART within the first six months after the first visit. *Not recommended, but acceptable according to experts opinion. ** Modifications to the guidelines in September 2008 were taken into account from 2009.

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

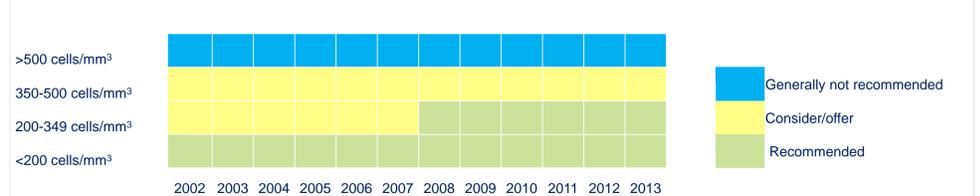


Figure 4: Evolution of CD4+ count criteria for starting ART in asymptomatic HIV infected individuals, according to the German-Austrian HIV treatment guidelines (2002-2012).

Conclusion

The majority of patients below the CD4 threshold of applicable guidelines received treatment within six months of presentation. Based on our observation, we predict that a considerable share of newly presenting patients will be affected by results of the START trial. However, we observed a slowly diminishing, but significant proportion of patients not started timely on ART, despite a CD4 count under the recommended threshold, potentially precluding them from advantages of early treatment.