Key Factors for Treatment Changes within One Year after Starting cART in the German ClinSurv Cohort between 2005 and 2014

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Background

- Initiation of combined antiretroviral therapy (cART) has markedly increased survival and quality of life in people living with HIV/AIDS (PLWHA) [1;2].
- In 2016, approximately 36.7 million people were living with HIV. As of October 2017, 20.9 million people were accessing cART [3].
- The effectiveness of cART is commonly measured by its ability to durably suppress HIV replication and to affect immune system reconstitution, which in turn result in decreased rates of HIV clinical progression, AIDS-related opportunistic diseases, and death.
- With the advent of new treatment options, including fixed-dose combinations and an increasing number of single-tablet combinations, the durability of first-line cART regimes is developing [4].
- These newer therapies have been associated with greater efficacy, tolerability, and convenience.

Objective

Our objective was to assess predictors of first-line cART treatment changes within the German ClinSurv cohort between 2005 and 2014

Methods

- We used data from the prospective multicenter German Clinical Surveillance of HIV Disease (ClinSurv) cohort of the Robert-Koch-Institute (RKI).
- Inclusion criteria were PLWHA, aged >18 years, who initiated cART as first-line therapy between 2005 and 2014.
- Sociodemographic and geographic data were used to characterize our study population (**Table1**).
- Time to event was calculated as time between initiation of first-line cART and therapy change.
- A Cox proportional hazard model was used to assess predictors of treatment change after starting cART.

Results

Population characteristics:

- We included 6,894 patients who initiated cART between 2005 and 2014.
- The sample population was predominantly men (79%) with German origin (69.8%), of which 49.6% were men reporting sex with men (MSM) as main risk factor (**Table 1**).
- The median (IQR) age was 38 (31-46) years.
- Median (IQR) length of time between first intake and stop of the cART regime was 30 (13-57) months.
- A total of 3,016 (43.7%) PLWHA stopped or changed their first-line cART between 2005 and 2014.
- Reasons for treatment changes were reported by 2,392 (34.7%) (**Figure 2**).

Table 1: Patient characteristics, median time to stop/change cART (months) and baseline characteristics (Kaplan-Meyer method) with overall comparison using Log-rank test.

	No of patients, n (%)	Median time (months) to stop/change first-line cART (IQR)	Overall comparison p-value**
Total	6,894 (100)		
Age (Median, IQR)	38 (31-46)		0.431
18-45	5,043 (73.2)	71 (65-76)	
>45	1,851 (26.8)	71 (62-78)	
Sex			<0.001
Female	1,445 (21.0)	75 (70-81)	
Male	5,449 (79.0)	49 (40-57)	
Risk group*			<0.001
MSM	3,420 (49.6)	78 (70-87)	
HTS	2,063 (29.9)	67 (61-74)	
PWID	397 (5.8)	46 (33-58)	
Other/ Unknown	1,014 (14.7)	69 (58-79)	
Country of origin			0.006
Germany	4,812 (69.8)	73 (67-78)	
Europe	534 (7.7)	63 (51-74)	
Africa	884 (12.8)	64 (50-77)	
Others	593 (9.0)	77 (61-93)	
CD4+ T cell count/µl at baseline (Median, IQR)	250 (124-372)		<0.001
<200	2,674 (38.8)	62 (56-69)	
200 – 349	2,234 (32.4)	78 (70-87)	
350 – 499	1,194 (17.3)	71 (62-80)	
>500	792 (11.5)	85 (63-108)	
HIV-1 RNA (copies/ml) at baseline (Median, IQR)	32,461 (1,159-156,170)		<0.001
<9,999	2,600 (37.7)	70 (64-77)	
10,000 - 99,999	2,044 (29.6)	75 (66-84)	
>100,000	1,935 (28.1)	71 (62-79)	
>1mio.	315 (4.6)	32 (20-44)	
Year of ART start			0.077
2005-2006	1,357 (19.7)	61 (52-71)	
2007-2008	1,730 (25.1)	75 (68-80)	
2009-2010	1,910 (27.7)	62 (61-64)	
2011-2012	1,649 (23.9)	n.a.	
2013-2014	248 (3.6)	n.a.	
First-line regimens			<0.001
2NRTI/1PIr	3,314 (48.1)	56 (52-61)	
2NRTI/1NNRTI	2,910 (42.2)	n.a.	
2NRTI/1II	361 (5.2)	n.a.	
Others	309 (4.5)	14 (11-19)	

* MSM, men who have sex with men; HTS, heterosexual; PWID, persons who inject drugs
** Log-rank overall comparison (p<0.05)

Results

- The most frequently used treatment combinations were 2NRTI/PIr 48.1% (n=3,314), 2NRTI/1NNRTI 42.2% (n=2,910), and 2NRTI/1II 5.2% (n=361) (**Figure 1**).
- The most common documented causes were side effects of drugs 41.0% (n=974), non-adherence 16% (n=386) and the simplification of therapy 12% (n=300) (**Figure 2**).

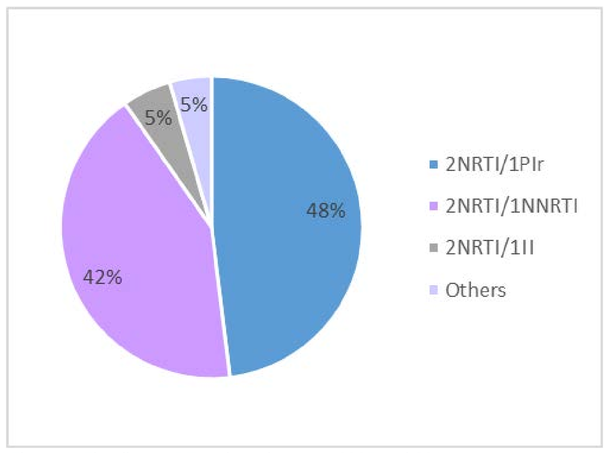

Figure 1: First-line cART regimes between 2005 and 2014 (n= 6,894).

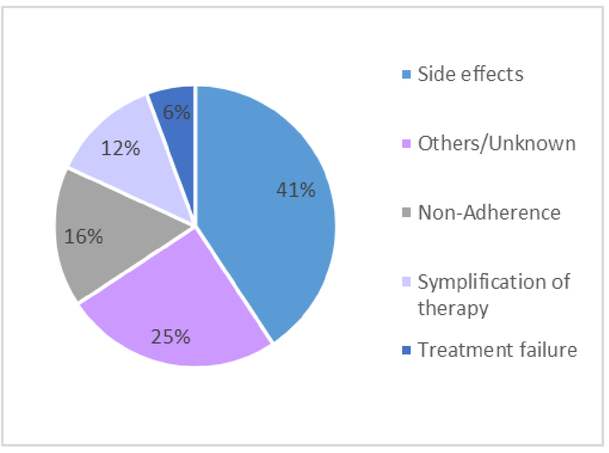

Figure 2: Reported reasons to change/stop the first-line cART reported between 2005-2014 (n= 2,392).

Time to events analysis:

- Statistically significant differences in time to stop or change first-line cART regime were observed regarding sex (p<0.001); CD4+ T cell count and viral load at baseline (p<0.001); reported risk group (p<0.001) and cART regime (p<0.001) (**Figure 3**).

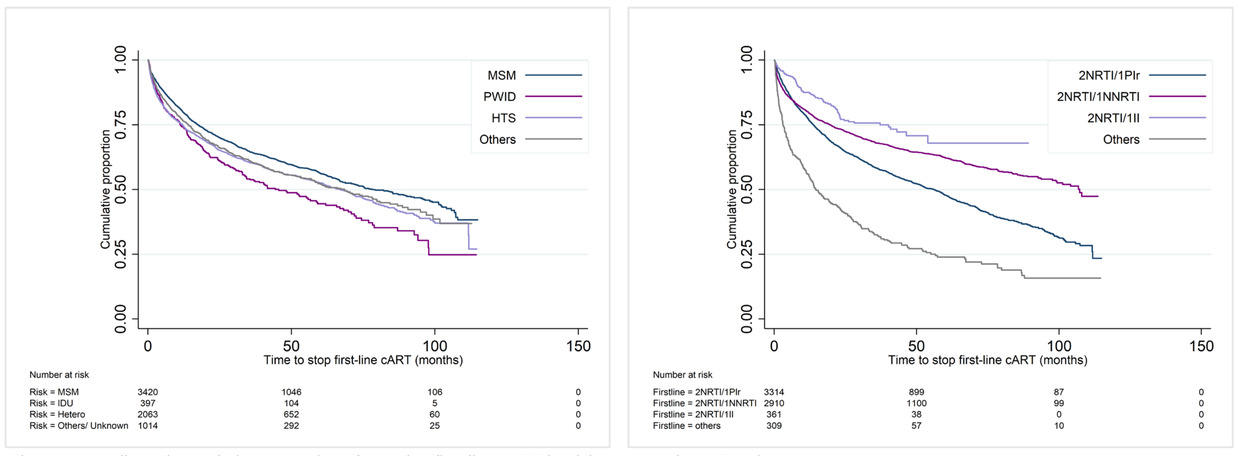

Figure 3: Unadjusted cumulative proportion of stopping first-line cART by risk group and cART regime.

Cox regression:

- In the Cox-regression model, we identified numerous significant covariates associated with discontinuation of the first-line regime.
- A 2NRTI/1II regime was associated with lower rates (HR 0.34, 95% CI 0.23-0.51) of treatment modification compared 2NRTI/1PIr).
- The HR increased markedly with the amount of daily-administered tablets from HR 1.39, 95% CI 1.09-1.77 (2-3 tablets) to HR 2.08, 95% CI 1.37-3.15 (10 tablets) (ref.: one tablet).
- Administration of cART twice a day, resulted in increased numbers of treatment change with an HR of 1.59 (95% CI 1.41-1.79) (ref.: once per day).
- An association was also observed in patients with a baseline viral load (VL) of > 1 Mio. copies/ml (HR 1.41, 95%CI 1.19-1.66) and >100,000 copies/ml (HR 1.02, 95% CI 0.90-1.12) (ref.: VL <10,000. copies/ml).
- Men were more likely to change cART regime compared to women (HR 1.35, 95% CI 1.21-1.50).

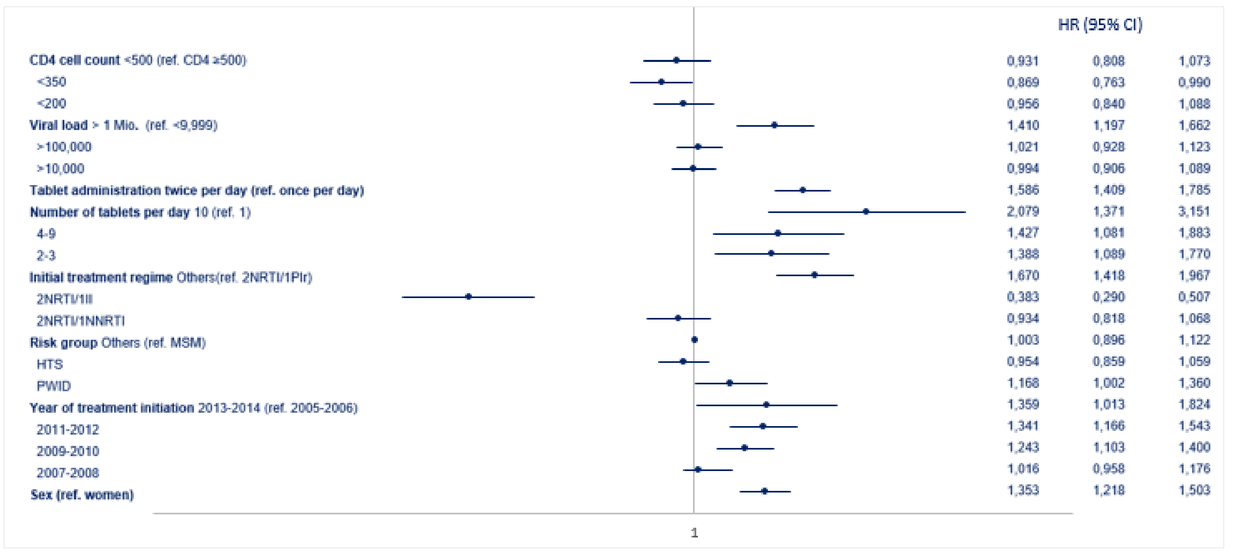

Figure 4: Hazard ratios (HRs) and 95% confidence intervals (CI) associated with discontinuation of cART from the final Cox model adjusted for gender, age, year of cART initiation, number of tablets per day, tablet administration per day, viral load and CD4+ T cell count at time of cART initiation, risk group, cART regime and country of origin.

Conclusion

- In our analysis of the German national ClinSurv cohort, we identified numerous significant covariates associated with discontinuation of the first line cART regime between 2005 and 2014.
- A VL of > 1 Mio. at baseline, tablet administration twice per day, a larger amount of daily-administered tablets and the year of treatment initiation were significantly associated with treatment change.
- Understanding the complex interplay of factors more clearly is essential for clinicians and healthcare decision-makers to be able to achieve the level of adherence required to effectively enhance the first-line cART regime.

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