Selected comorbidities and the risk of ART switch in the context of HIV-RNA suppressed to ≤50 copies/mL

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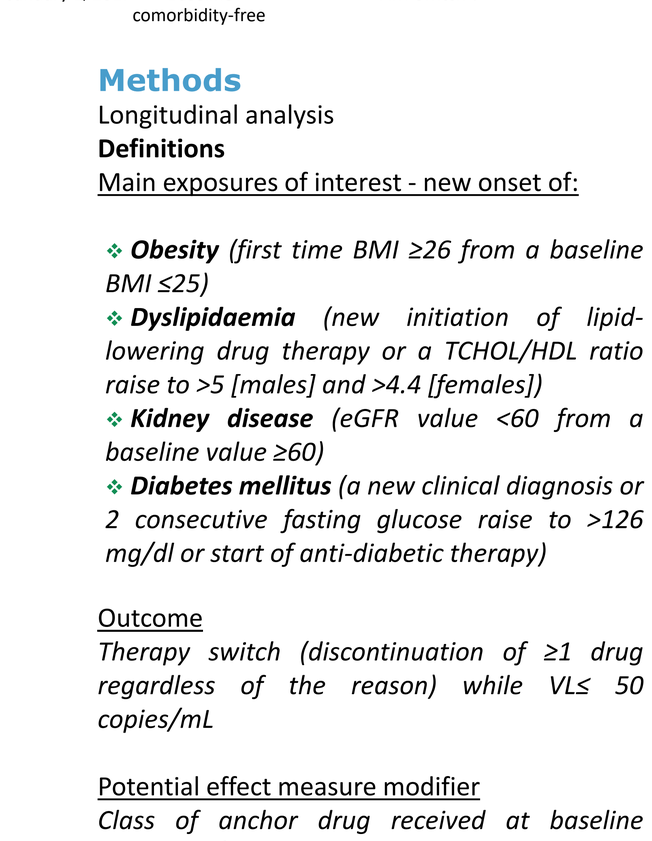
Background

- Although HIV-associated mortality has been greatly reduced by ART, the incidence of deaths due to non-communicable diseases (NCDs) remains high in persons with HIV (PWH)
- More than half of the deaths observed in recent years among ART-experienced PLHIV are attributable to NCDs/comorbidities
- NCDs include cardiovascular disease, hypertension, osteoporosis, kidney and liver failure, diabetes mellitus, cancer and other comorbidities such as central nervous system disorders.
- Clinical decisions regarding whether to modify ART in the context of a HIV-RNA≤50 copies/mL may be guided by current ART and specific comorbidities

Objectives

- To describe demographics, HIV-related, and clinical characteristics of PWH with HIV-RNA ≤50 copies/mL undergoing a therapy switch, regardless of the reason of switch
- To estimate the association between the new onset of the following co-morbidities and the the risk of experiencing a therapy switch:
  - **Obesity**
  - **Dyslipidaemia**
  - **Kidney disease**
  - **Diabetes mellitus**
- To evaluate whether these associations may vary by class of anchor drug

Figure 1 Study Population and analysis design



Methods

Longitudinal analysis

Definitions

Main exposures of interest - new onset of:

- ***Obesity*** *(first time BMI ≥26 from a baseline BMI ≤25)*
- ***Dyslipidaemia*** *(new initiation of lipid-lowering drug therapy or a TCHOL/HDL ratio raise to >5 [males] and >4.4 [females])*
- ***Kidney disease*** *(eGFR value <60 from a baseline value ≥60)*
- ***Diabetes mellitus*** *(a new clinical diagnosis or 2 consecutive fasting glucose raise to >126 mg/dl or start of anti-diabetic therapy)*

Outcome

Therapy switch (discontinuation of ≥1 drug regardless of the reason) while VL≤ 50 copies/mL

Potential effect measure modifier

Class of anchor drug received at baseline (NNRTI, PI/r, INSTI)

Statistical analysis

- Demographics, HIV-related, and clinical characteristics at baseline were described and stratified by selected concomitant co-morbidities at baseline
- Incidence of new onset of comorbidity/ART switch was estimated using the Kaplan-Meier method
- A separate standard Cox regression model was fitted with comorbidities fitted as a time-varying covariate to estimate hazard ratios (HR) of ART switch after controlling for baseline time-fixed confounding (see list at bottom of Table 3)
- Statistical interaction between the exposure variable (that is, new onset comorbidity) and the anchor drug in the baseline ART regimen was formally tested by including an interaction term in the Cox regression models
- In case of evidence of interaction, results were stratified by anchor drug class received at baseline

Results

- For convenience, the descriptive analyses are shown for the dyslipidemia-free cohort only. In this study population, we found little evidence for a difference in baseline characteristics between participants who developed dyslipidemia over time and those who did not, with the exception of calendar year (incidence of dyslipidemia was higher in more recent years, Table 1).
- The results of the Cox regression analysis are controlled for this imbalance

	Incident dyslipidaemia (all)			
Characteristics at baseline	Yes N= 245	No N= 877	p-value*	Total N= 1122
Gender, n(%)			0.204	
Female	39 (15.9%)	171 (19.5%)		210 (18.7%)
Mode of HIV Transmission, n(%)			0.699	
PWID	18 (7.5%)	59 (6.9%)		77 (7.0%)
Homosexual contacts	110 (45.6%)	430 (50.0%)		540 (49.0%)
Heterosexual contacts	99 (40.4%)	325 (37.1%)		424 (37.8%)
Other/Unknown	14 (5.8%)	46 (5.3%)		60 (5.4%)
Nationality, n(%)			0.574	
Not Italian	159 (64.9%)	552 (62.9%)		711 (63.4%)
AIDS diagnosis, n(%)			0.554	
Yes	26 (10.6%)	82 (9.4%)		108 (9.6%)
HBsAg, n(%)			0.875	
Positive	1 (0.4%)	6 (0.7%)		7 (0.6%)
HCVAb, n(%)			0.992	
Positive	17 (6.9%)	62 (7.1%)		79 (7.0%)
Calendar year of baseline	2020 (2018, 2021)	2019 (2017, 2020)	<.001	2019 (2018, 2020)
Age, years			0.09	
Median (IQR)	42 (33, 50)	40 (31, 50)		40 (32, 50)
CD4 count, cells/mm³				
Median (IQR)	645 (423, 861)	643 (461, 876)	0.60	644 (450, 872)
≤200	8 (3.3%)	33 (3.8%)	0.71	41 (3.7%)
CD4 count nadir, cells/mm³				
Median (IQR)	342 (168, 544)	353 (189, 524)	0.60	352 (181, 527)
egfr (CKD_Epi formula), ml/min/1.73m²				
Median (IQR)	94.73 (83.60, 107.8)	95.52 (81.26, 109.1)	0.98	95.39 (81.48, 108.6)
< 60, n(%)	16 (6.5%)	41 (4.7%)	0.24	57 (5.1%)
Smoking, n(%)			0.16	
No	95 (38.8%)	397 (45.3%)		492 (43.9%)
Yes	89 (36.3%)	272 (31.0%)		361 (32.2%)
Duration of VL suppression, months				
Median (IQR)	8.6 (7.0, 13.3)	8.6 (6.9, 12.4)	0.66	8.6 (6.9, 12.5)

Table 2. Incidence of new comorbidities

Kaplan-Meier estimates (95% CI) by 24 months from baseline

	N	Cum Prob	95% CI
Exposure			
Obesity	39	9.2%	6.3% - 12.2%
Dyslipidaemia	111	17.6%	14.4% - 20.8%
Kidney disease	61	8.9%	6.6% - 11.2%
Diabetes mellitus	2	0.3%	0.0% - 0.8%
Outcome (ART switch)			
Obesity model	254	47.0%	42.6%-51.3%
Dyslipidaemia model	376	45.1%	41.5% - 48.6%
Kidney disease model	443	45.4%	42.1% - 48.7%
Diabetes mellitus model	442	46.1%	42.8% - 49.4%

- From fitting a standard Cox regression model with time-fixed covariates measured at baseline we found a >4-fold higher risk of therapy switch associated with the development of diabetes, although not statistically significant (p=0.22, Table 3).
- The development of dyslipidemia was associated with a >2-fold higher risk of therapy switch but only when restricting the analysis to participants who were receiving a PI-based therapy (interaction p-value=0.04, Table 3). We found no evidence for an association with the development of renal disease or obesity.

Table 3. Hazard rations (HR) of therapy switch from fitting a Cox regression model

	Hazard Ratio (95% CI) p-value	
	Unadjusted	Adjusted
Becoming diabetic		
No	1.00	1.00
Yes	3.84 (0.32, 46.48)	4.69[1] (0.40, 54.81)
	0.290	0.218
Developing dyslipidaemia (all)		
No	1.00	1.00
Yes	1.09 (0.86, 1.39)	1.08[2] (0.84, 1.40)
	0.473	0.550
Developing dyslipidaemia (PI-based)		
No	1.00	1.00
Yes	2.17 (1.18, 4.00)	2.30[2] (1.06, 4.99)
Experiencing a eGFR below 60		
No	1.00	1.00
Yes	0.71 (0.42, 1.19)	0.74[3] (0.44, 1.26)
	0.194	0.274
BMI less than 25 to 26+		
No	1.00	1.00
Yes	0.79 (0.46, 1.34)	0.76[4] (0.44, 1.32)
	0.383	0.334

[1]Adjusted for baseline calendar year, age, dyslipidaemia, obesity and nationality
[2]Adjusted for baseline calendar year, age, sex, obesity, alcohol use and nationality
[3]Adjusted for baseline calendar year, age, diabetes and sex
[4]Adjusted for baseline calendar year, age, sex and nationality

Limitations

- Time-varying confounding has been ignored (e.g. the analysis of the risk associated with dyslipidaemia ignores the use of lowering-lipid drugs after baseline)
- We cannot rule out unmeasured confounding
- Estimates from the Cox models are valid under the assumption of a correctly specified model (linear predictor, all baseline confounders accounted for, etc.)
- For rare comorbidities (i.e. diabetes) and in general to detect interactions, analysis is likely to be underpowered and needs to be repeated when a larger number of ART switch cumulates
- We have not investigated reasons for switching and described the regimens that were initiated after the switch

Conclusions

- **Overall, approximately 45% of participants underwent a ART switch by 24 months in our setting of VL≤50 copies/mL**
- **Among the co-morbidities considered, dyslipidaemia had the higher incidence while new onset of diabetes was very rare**
- **The development of diabetes over follow-up appeared to be associated with a >4-fold greater risk of modification of participants' ART regimen composition, although with large uncertainty around the estimate**
- **Newly onset of dyslipidaemia was also a risk factor for ART modification (>2 fold increased risk) although only in participants receiving PI-based regimens**
- **Newly development of these conditions in PWH with VL≤50 copies/mL should be carefully monitored as they appear to be a trigger for therapy modifications**

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