Chronic liver inflammation and use of contemporary ART among persons living with HIV

RESPOND International Cohort Consortium of Infectious Diseases

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BACKGROUND

- ART has increased life expectancy for persons living with HIV (PLWH), yet PLWH have 16.3 fewer healthy years than their HIV negative counterparts.[1]
- Liver disease in PLWH accounts for 13-18% of all cause mortality, a leading cause of co-morbidity and non-AIDS related death.[2-4]
- Chronic liver enzyme elevation (cLEE) is common in PLWH with and without viral hepatitis B or C (HBV/HCV), yet the clinical significance remains unclear.
- The START trial found early ART may lower liver fibrosis compared to deferring ART[5]
- The D:A:D study found cumulative exposure to older drugs (d4T, ddl, APV, TDF*) were associated with cLEE[6], but there are limited data on cLEE with newer ARVs.
- Data from the NHS study showed that INSTIs could be protective against cLEE[7], but N was small, N =2779.

AIM

- To identify risk factors associated with cLEE and contemporary ART use.

METHODS

- Data: RESPOND, a large PLWH international cohort collaboration in Europe and Australia with over 30,000 individuals under active follow-up.
- Individuals were included starting Jan 1, 2012 who started an ARV to which they had not been previously exposed, the new ARV start date was the study baseline.
- ARVs considered were*
  - INSTIs; DTG, EVG/c, RAL, BIC
  - NNRTIs: EFV, RPV
  - NRTIs: TAF, TDF
  - PIs: DRV/b, any ATV
- Individuals must have had ≥1 HIV-RNA ,CD4 cell count and alanine transaminase (ALT) 1 year before baseline, with all aforementioned ALTs in the normal range
- The primary outcome was first cLEE
  - ALT elevations > than the upper limit of normal (males >50 IU/L; females >35 IU/L) at 2 visits at least 6 months, but no more than 2 years apart[9]
- Using an intention to treat approach (ITT), individuals were censored at the first of: cLEE, last visit, death, or Dec 31 2020.
- Incidence rates (IR) (events/1000 person-years follow-up (PYFU)) were calculated for each ARV overall and by ARV exposure (6-12 months, 1-2 years, and 2+ years) to investigate cumulative effects.
- Poisson regression was used to estimate the incidence rate ratio (IRR) of cLEE and its association with individual ARVs and ARV class.

*ARV Abbreviations: APV – Amprenavir; ddl – Didanosine; d4T – Stavudine; INSTI - Integrase strand transfer inhibitors; DTG – Dolutegravir; EGV/c – Elvitegravir; RAL – Raltegravir; BIC - Bictegravir; NNRTI - Non-nucleoside reverse transcriptase inhibitors; EFV – Efavirenz; RPV – Rilpivirine; NRTI - Nucleoside reverse transcriptase inhibitors; TAF – Tenofovir alafenamide; TDF - Tenofovir disoproxil fumarate; PI - Protease inhibitors; DRV/b – Darunavir; ATV – Atazanavir.

RESULTS

- 14,481 individuals contributed 59,798 PYFU, median (IQR) 4.05 (2.34, 5.82) years, Table
- 1427 experienced cLEE: IR (95%CI) = 23.8 (22.7,22.1)/1000 PYFU

Table: Study Characteristics

		Total 14,481		cLEE 1427	
		N	%	N	%
Gender	Male	10975	75.8	1062	74.4
	Female	3476	24	362	25.4
	Other/Unknown	30	0.2	3	0.2
Ethnic Origin	White	10473	72.3	1059	74.2
	Black	1499	10.4	112	7.8
	Other	519	3.6	61	4.3
	Unknown	1990	13.7	195	13.7
HIV Risk Group	MSM	6967	48.1	666	46.7
	IDU	1473	10.2	165	11.6
	Heterosexual	5154	35.6	511	35.8
	Other	340	2.3	30	2.1
	Unknown	547	3.8	55	3.9
Region of Care	Western Europe	8234	56.9	822	57.6
	Southern Europe	3362	23.2	282	19.8
	Northern Europe†	1724	11.9	165	11.6
	Eastern Europe	1161	8	158	11.1
HCV/HBV positive		2626	18.1	304	21.3
Age at baseline median (IQR)		47	(38, 55)	45	(37, 52)
Baseline CD4 nadir median (IQR)		244	(125, 373)	234	(116, 369)
Baseline RNA median (IQR)		1.6	(1.3, 4.2)	1.6	(1.3, 4.2)
Follow-up years median (IQR)		4.05	(2.34, 5.82)	1.84	(1.03, 3.37)
Baseline ALT median (IQR)		23	(18, 30)	28	(22, 36)

† Northern Europe and Australia

Figure 1: IR (95% CI) of cLEE by time since new ARV initiation

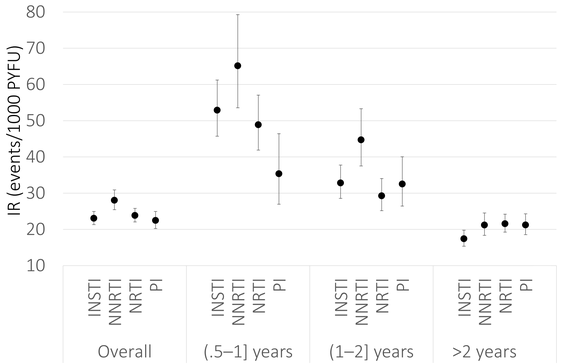
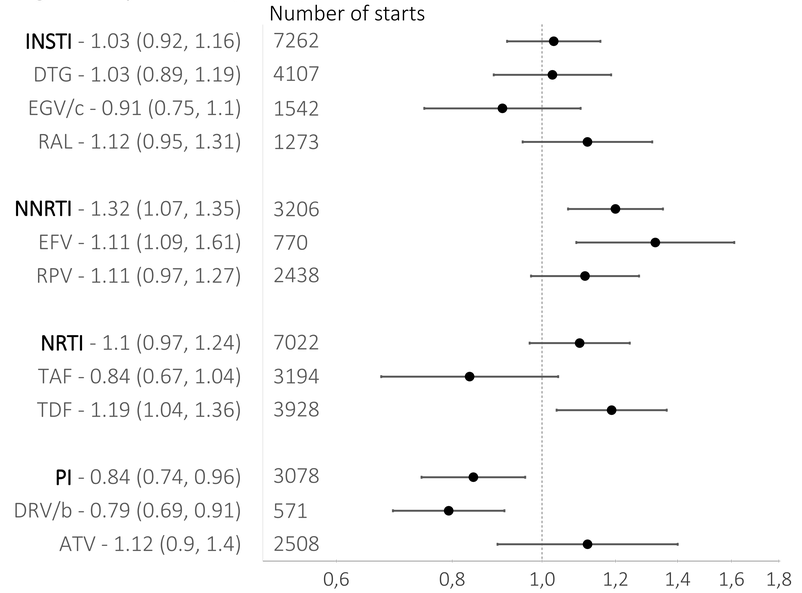


Figure 2: Adjusted[α] IRR (95% CI) of cLEE



[α] The reference group for each model is no previous exposure to that drug. BIC, any ATV, and doravirine did not have enough events/follow-up to analyse individually. All models adjusted for viral hepatitis status, nadir CD4 at baseline (<350, 350-500, ≥500 cells/mm^3), HIV-RNA at baseline (<200, ≥ 200 copies/ml) , HIV transmission risk group (men who have sex with men, injection drug use, heterosexual, other, unknown), region of care (Western, Southern, Northern, Eastern Europe), dyslipidemia (random total cholesterol more than 240 mg/dl, HDL less than 35 mg/dl, triglyceride more than 200 mg/dl, or initiation of lipid-lowering therapy), diabetes mellitus, and BMI (<25, ≥25, missing).

RESULTS CONTINUED

- There was no evidence of a cumulative effect of ARV on cLEE, Figure 1
- Any use (vs. no prior use) of EFV and TDF were independently associated with an increased IRR of cLEE, Figure 2
- DRV was associated with a decreased risk of cLEE, Figure 2.
- No INSTI was associated with cLEE

SENSITIVITY ANALYSES

- Similar results were seen when conducting an on-treatment analysis (censoring at any treatment changes) and among those ARV naïve in both ITT and on treatment approaches

LIMITATIONS

- Potential for unmeasured confounding
- Possibility for unmeasured drug-drug interactions that are not adequately measured in RESPOND
- Not enough power to investigate individual drugs among those with viral hepatitis and among ARV naïve
- Whether cLEE translates into clinically relevant outcomes (all-cause/liver related mortality) requires further follow-up
- This is a retrospectively defined observational study and not an RCT

CONCLUSIONS

- This is the first large study systematically looking at contemporary ARVs and cLEE
- cLEE is common, especially during the first year after initiating new ARVs
- With 4 years median follow-up, we found no short-term liver safety concerns with the use of INSTIs even after adjusting for confounders including HCV/HBV, BMI, CD4, HIV-RNA
- Use of EFV and TDF remain associated with an increased cLEE risk
- TAF and DRV utilization are associated with lower risks of cLEE, although TAF not statistically significant.

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