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Efficacy, safety and convenience of INSTI-based ART regimens in people living with HIV co-infected with hepatitis C and/or B viruses

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Background. Limited studies exist to describe the performance outcomes of integrase strand transfer inhibitors (INSTI) among persons living with HIV (PLWH) by their hepatitis coinfection status. The purpose of this study was to compare the efficacy, safety, and convenience of INSTI-based ART regimens in a large cohort of PLWH by hepatitis infection status (coinfected vs. not) using survival analysis.

Material and methods. We used data from 4942 subjects (of which 1709 coinfected with hepatitis viruses) enrolled in the Italian MaSTER cohort which systematically collects data at three time points (baseline, six and 12 months). The patients were categorized by hepatitis infection status, ART status (naives vs experienced) and regimens (three or two drug regimen). Three different metrics were used to study antiretroviral therapy (ART) interruptions: efficacy, defined as interruption due to inability to achieve or maintain viral suppression; safety, defined as interruption linked to laboratory alterations and/or clinical progression, and convenience, defined as absence of HIV RNA above 50 cp/ml and no laboratory alterations and/or clinical progression until INSTI-based ART regimen interruption.

Cox proportional hazards regression models were fitted to associate sociodemographic and clinical factors with performance outcomes stratified by hepatitis status.

Results. In the analysis of ART interruption due to efficacy or safety concerns, the hazards were higher among individuals with injection drug use (IDU) risk compared to individuals with heterosexual (HET) risk and for ART naives vs experienced individuals. In the analysis of ART interruptions due to inconvenience, higher hazards were observed among MSM compared to HET individuals and persons with three-drug regimens (3DR) compared to two-drug regimens (2DR). Additionally PLWH coinfected with HBV had higher hazards of treatment interruption (HR=2.75; CI=1.13-6.71), whereas PLWH with HCV had lower hazards of treatment interruption due to convenience (HR=0.77; CI=0.67-0.88).

Efficacy: Status(1) = VL >50 HIV RNA copies/ml

			Total population	Not coinfected	HCVorHBV coinfection
			Adjusted Hazard Ratio	Adjusted Hazard Ratio	Adjusted Hazard Ratio
	Age (years)		0.98 (0.97-1)	0.98 (0.97-1)	0.98 (0.95-1.01)
Sex	Male *vs. Female*		1 (0.79-1.28)	1.05 (0.76-1.45)	0.93 (0.64-1.36)
Nationality	Foreign-born *vs. Italian*		1.1 (0.78-1.54)	1.11 (0.77-1.61)	0.84 (0.31-2.31)
Risk	IDU *vs. HET*		1.84 (1.27-2.67)	1.84 (1.07-3.18)	1.71 (0.9-3.22)
	MSM *vs. HET*		0.85 (0.59-1.23)	0.88 (0.6-1.3)	0.49 (0.14-1.77)
	Other *vs. HET*		1.46 (1.05-2.03)	1.41 (0.98-2.03)	1.32 (0.56-3.13)
	HIV diagnosis year		1.04 (0.93-1.16)	0.96 (0.83-1.12)	1.15 (0.97-1.37)
	Baseline HIV-RNA(cp/ml)		1.15 (1.12-1.18)	1.17 (1.13-1.22)	1.13 (1.09-1.18)
	Baseline CD4		1 (1-1)	1 (1-1)	1 (1-1)
	Baseline CD8		1 (1-1)	1 (1-1)	1 (1-1)
ART status	Naïve *vs. Experienced*		1.88 (1.25-2.82)	2.07 (1.32-3.27)	7.25 (0.99-53.27)
Regimen	3D *vs. 2D*		0.99 (0.78-1.24)	0.99 (0.72-1.35)	1.02 (0.72-1.43)
INSTI initiation cohort	2012-14 *vs. 2009-11*		1.36 (0.85-2.15)	1.15 (0.61-2.19)	1.57 (0.78-3.15)
	2015-17 *vs. 2009-11*		0.96 (0.48-1.95)	1.19 (0.47-2.99)	0.71 (0.23-2.15)
	Duration of INSTI		1.04 (0.94-1.16)	0.95 (0.83-1.1)	1.16 (0.98-1.38)
Baseline HBV+ *vs. non-infected*			0.72 (0.39-1.31)	--	0.84 (0.4-1.79)
Baseline HCV+ *vs. non-infected*			0.79 (0.56-1.11)	--	1.03 (0.39-2.74)

Safety: Status(1) = laboratory alterations of grade 3-4 and/or clinical progression

Total population	Not coinfected	HCVorHBV coinfection
Adjusted Hazard Ratio	Adjusted Hazard Ratio	Adjusted Hazard Ratio
1.03 (1.02-1.04)	1.03 (1.03-1.04)	1.02 (1.01-1.04)
0.93 (0.82-1.06)	0.96 (0.8-1.14)	0.88 (0.73-1.06)
1 (0.82-1.22)	0.96 (0.76-1.21)	1.25 (0.82-1.89)
1.24 (1.04-1.49)	1.54 (1.14-2.08)	1.06 (0.83-1.37)
1.07 (0.91-1.26)	1.08 (0.9-1.29)	0.91 (0.63-1.3)
1.1 (0.93-1.31)	1 (0.82-1.23)	1.19 (0.85-1.65)
1.41 (1.33-1.5)	1.62 (1.49-1.76)	1.25 (1.15-1.36)
1.02 (1-1.04)	1.02 (0.99-1.04)	1.03 (1-1.05)
1 (1-1)	1 (1-1)	1.21 (0.88-1.66)
1 (1-1)	1 (1-1)	0.96 (0.66-1.4)
1.54 (1.16-2.04)	1.66 (1.17-2.34)	1 (1-1)
1.07 (0.95-1.2)	0.9 (0.77-1.05)	1 (1-1)
0.6 (0.46-0.78)	0.35 (0.24-0.53)	1.12 (0.64-1.96)
0.49 (0.33-0.71)	0.32 (0.19-0.55)	1.28 (1.07-1.53)
1.41 (1.33-1.49)	1.6 (1.47-1.74)	0.9 (0.62-1.3)
1.35 (1.09-1.68)	--	0.66 (0.38-1.15)
1.09 (0.93-1.28)	--	1.26 (1.16-1.37)

Convenience: Status(1) = VL <50 HIV RNA copies/ml + no laboratory alteration

Total population	Not coinfected	HCVorHBV coinfection
Adjusted Hazard Ratio	Adjusted Hazard Ratio	Adjusted Hazard Ratio
0.99 (0.98-1)	1 (0.99-1.01)	0.96 (0.94-0.98)
0.61 (0.51-0.73)	0.52 (0.4-0.67)	0.72 (0.55-0.95)
1.12 (0.87-1.44)	1.06 (0.8-1.42)	1.27 (0.72-2.23)
1.09 (0.83-1.45)	1.38 (0.83-2.29)	0.8 (0.56-1.16)
1.22 (0.96-1.55)	1.51 (1.14-2)	0.54 (0.28-1.03)
0.87 (0.65-1.15)	0.95 (0.69-1.32)	0.63 (0.35-1.13)
0.86 (0.79-0.93)	0.91 (0.82-1.02)	0.77 (0.67-0.88)
1.03 (1-1.05)	1.03 (1-1.07)	1.02 (0.98-1.06)
1 (1-1)	1 (1-1)	1.26 (0.74-2.15)
1 (1-1)	1 (1-1)	1.34 (0.7-2.53)
0.94 (0.68-1.28)	0.99 (0.68-1.43)	1 (1-1)
1.94 (1.57-2.39)	1.9 (1.43-2.52)	1 (1-1)
1.43 (0.99-2.05)	1.39 (0.86-2.23)	1.26 (0.59-2.65)
1.28 (0.74-2.24)	0.83 (0.4-1.71)	1.9 (1.38-2.63)
0.83 (0.77-0.91)	0.87 (0.78-0.98)	1.55 (0.86-2.78)
1.09 (0.74-1.59)	--	2.75 (1.13-6.71)
1.23 (0.97-1.58)	--	0.77 (0.67-0.88)

Durability: Status(1) = interruption regardless of VS, lab alt, or clinical progression

Total population	Not coinfected	HCVorHBV coinfection
Adjusted Hazard Ratio	Adjusted Hazard Ratio	Adjusted Hazard Ratio
1 (0.99-1.01)	1 (1-1.01)	0.99 (0.97-1)
0.71 (0.63-0.82)	0.69 (0.57-0.83)	0.75 (0.62-0.91)
1.13 (0.93-1.37)	1.1 (0.88-1.37)	1.25 (0.83-1.91)
1.23 (1-1.5)	1.93 (1.4-2.66)	0.83 (0.64-1.08)
1.09 (0.9-1.31)	1.25 (1.01-1.54)	0.58 (0.36-0.93)
0.97 (0.8-1.19)	1.03 (0.81-1.3)	0.67 (0.45-0.99)
0.84 (0.79-0.9)	0.88 (0.81-0.96)	0.8 (0.73-0.88)
1.05 (1.03-1.07)	1.06 (1.04-1.09)	1.04 (1.02-1.07)
1 (1-1)	1 (1-1)	1.09 (0.75-1.59)
1 (1-1)	1 (1-1)	1.18 (0.76-1.83)
1.08 (0.86-1.36)	1.17 (0.88-1.54)	1 (1-1)
1.46 (1.27-1.67)	1.31 (1.08-1.58)	1 (1-1)
1.69 (1.32-2.17)	1.46 (1.03-2.08)	1.36 (0.8-2.31)
0.99 (0.66-1.49)	0.76 (0.44-1.32)	1.6 (1.31-1.97)
0.83 (0.78-0.88)	0.85 (0.79-0.93)	2.03 (1.41-2.93)
1.11 (0.85-1.46)	--	1.38 (0.75-2.54)
1.18 (0.99-1.42)	--	0.79 (0.73-0.87)

Cox proportional hazard regression analysis

Conclusions. To our knowledge, this was the first study to investigate the performance outcomes of INSTI-based ART regimens by hepatitis status. We observed different hazards of treatment interruption by hepatitis status. These results warrant further research on this topic.

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