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Initial plasma HIV-1 RNA and CD4+ T-cell count are determinants of virological outcomes with initial integrase inhibitor-based regimens: a prospective multinational RESPOND cohort consortium.

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Background and Aim

There are conflicting data regarding baseline determinants of virological non-suppression outcomes in people living with HIV who initiate antiretroviral treatment (ART). We evaluated the impact of different baseline variables in the RESPOND cohort consortium.

Methods

We included treatment-naïve participants aged ≥18 who initiated 3-drug ART(two nucleos[t]ides and either dolutegravir, raltegravir, elvitegravir, darunavir or rilpirivine), 2014-2020. We assessed the odds of virological suppression (VS) (HIV-1 RNA <50 copies/mL) at week 48 and 96, using logistic regression. The incidence of viral blips (isolated HIV-1 RNA ≥50 copies/mL following VS), low-level viremia (LLV) (≥2 consecutive HIV-1 RNA 50-199 copies/mL following VS), residual viremia (RV) (HIV-1 RNA 20-49 copies/mL for assay with limit of detection of 20 copies/mL following VS) and virological failure (VF) (two consecutive HIV-1 RNA ≥50, one of them ≥200 copies/mL following VS) rates were assessed using Cox regression. The outcomes assessment was based on an intention-to-treat-exposed (ITT-e) analysis including all participants starting their first ART regimen in the defined period and having HIV-1 RNA in the relevant time point, imputing missing values as excluded.

Results

Out of 4,310 eligible participants, 72·3% initiated integrase inhibitor (INSTI)-based regimes, of whom 1,970 (63·3%) initiated dolutegravir (Table 1). VS at week 48 and 96 with a 12-week window on either side, and Kaplan-Meier estimates of the proportion with viral blips, LLV, RV and VF at 12 months were assessed (Table 2). In the multivariate analysis (Table 3 and Figure 1), baseline HIV-RNA >100,000 copies/mL and CD4+ count ≤200 cells/µL were negatively associated with VS at weeks 48 and 96, and with significantly higher rates of blips, LLV and RV. CD4+ count ≤200 cells/µL was associated with higher risk of VF. Results were consistent in those starting INSTIs compared to other regimens or those initiating dolutegravir compared to other INSTIs (p>0·05, tests for interaction).

Table 1. Baseline characteristics of participants in the Intention-to-treat exposed population.

	n=4,310
Gender · n (%)	
Male	3,614 (83·9)
HIV transmission route · n (%)	
MSM	2,636 (61·2)
Heterosexual	1,206 (28·0)
IDU	208 (4·8)
Other	260 (6·0)
Ethnicity· n (%)	
Caucasian	2,982 (69·2)
Other	555 (12·9)
Unknown	773 (17·9)
HBV (HBsAg)· n (%)	
Negative	3,257 (75·6)
Positive	113 (2·6)
Unknown	940 (21·8)
HCV (antibodies)· n (%)	
Negative	3,077 (71·4)
Positive	344 (8·0)
Unknown	889 (20·6)
Origin region· n (%)	
Southern Europe	1,461 (33·9)
Central Europe	1,835 (42·6)
Northern Europe/ Australia	609 (14·1)
Eastern Europe	405 (9·4)
Prior AIDS· n (%)	
Yes	438 (10·2)
Age at ART initiation (years old)· n (%)	
≤30	1,029 (23·9)
31-40	1,388 (32·2)
41-50	1,081 (25·1)
>50	812 (18·8)
Median age at ART initiation, years old (IQR)	38 (30-47)
Year of ART initiation · n (%)	
2014-15	1,866 (43·3)
2016-17	1,627 (37·7)
2018-19	817 (19·0)
HIV viral load at ART initiation (HIV-1 RNA copies/mL) · n (%)	
≤ 10,000	971 (22·5)
10,001- 99,999	1,782 (41·3)
100,000-500,000	986 (22·9)
>500,000	571 (13·2)
Median HIV-1 RNA $\log_{10}$ copies/mL (IQR)	4·7 (4·1-5·3)
CD4 + T-cell count at ART initiation (cells/µL)· n (%)	
≤100	633 (14·7)
101-200	459 (10·6)
201-350	879 (20·4)
351-500	988 (22·9)
>500	1,351 (31·3)
Median CD4+ T-cell count, cells/µL (IQR)	378 (199-560)
Initial ART · n (%)	
NRTI	
ABC/3TC	908 (21·1)
TDF/FTC	2,417 (56·1)
TAF/FTC	985 (22·9)
Third drug	
DRV	641 (14·9)
RPV	555 (12·9)
EVG/c	771 (17·9)
DTG	1,970 (45·7)
RAL	373 (8·7)

MSM, men who have sex with men; IDU, injection drug user; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; BMI, body mass index; AIDS, acquired immunodeficiency syndrome; NRTI, nucleos(t)ide reverse transcriptase inhibitor; ABC, abacavir; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; TAF, tenofovir alafenamide; DRV, darunavir; RPV, rilpivirine; EVG/c, elvitegravir/cobicistat; DTG, dolutegravir; RAL, raltegravir

Table 3. Logistic regression analysis (multivariate) of factors associated with virological suppression at week 48 and 96, for all participants included.

Virological outcomes	Virological suppression week 48		Virological suppression week 96	
	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Gender				
Male	1·0 (Ref)		1·0 (Ref)	
Female	1·16 (0·83-1·61)	0·40	0·81 (0·56-1·18)	0·27
Ethnicity				
Caucasian	1·0 (Ref)		1·0 (Ref)	
Other	0·80 (0·55-1·15)	0·23	0·80 (0·51-1·26)	0·34
HCV				
Negative	1·0 (Ref)		1·0 (Ref)	
Positive	0·46 (0·32-0·68)	**<0·001**	0·64 (0·38-1·05)	0·08
Origin region				
Southern Europe	1·0 (Ref)		1·0 (Ref)	
Central Europe	0·86 (0·65 -1·15)	0·32	1·00 (0·71-1·41)	0·99
Northern Europe/Australia	0·90 (0·60-1·34)	0·60	1·30 (0·80-2·12)	0·29
Eastern Europe	0·74 (0·45-1·21)	0·23	0·88 (0·44-1·75)	0·72
Baseline HIV viral load, HIV-1 RNA copies/mL				
≤10,000	1·19 (0·80-1·76)	0·39	1·41 (0·87-2·27)	0·16
10,001-100,000	1·0 (Ref)		1·0 (Ref)	
>100,000	**0·51 (0·39-0·68)**	**<0·001**	**0·69 (0·49-0·97)**	**0·03**
Baseline CD4+ T-cell count, cells/µL				
≤200	**0·40 (0·27-0·58)**	**<0·001**	**0·35 (0·22-0·55)**	**<0·001**
201-350	**0·58 (0·39-0·84)**	**<0·001**	**0·48 (0·30-0·76)**	**<0·001**
351-500	0·91 (0·60-1·38)	0·66	1·13 (0·67-1·93)	0·64
>500	1·0 (Ref)		1·0 (Ref)	
Prior AIDS				
No	1·0 (Ref)		1·0 (Ref)	
Yes	0·72 (0·52-1·00)	0·05	0·73 (0·48-1·12)	0·15
Age of ART initiation, years old				
≤30	1·0 (Ref)		1·0 (Ref)	
31-40	0·95 (0·68-1·34)	0·78	1·04 (0·68-1·58)	0·85
41-50	1·17 (0·81-1·67)	0·40	1·40 (0·88-2·21)	0·15
>50	0·87 (0·60-1·25)	0·44	0·77 (0·50-1·20)	0·26
Year of ART initiation				
2014-15	1·17 (0·87-1·58)	0·30	0·93 (0·65-1·34)	0·70
2016-17	1·0 (Ref)		1·0 (Ref)	
2018-19	0·74 (0·55-1·11)	0·14	0·68 (0·42-1·08)	0·10
NRTI				
ABC/3TC	0·85 (0·60-1·19)	0·34	**0·46 (0·30-0·69)**	**<0·001**
TDF/FTC	1·0 (Ref)		1·0 (Ref)	
TAF/FTC	1·19 (0·84-1·69)	0·33	0·97 (0·61-1·53)	0·88
Third drug				
DRV	**0·63 (0·45-0·87)**	**0·01**	0·65 (0·43-1·00)	0·05
RPV	0·99 (0·57-1·71)	0·96	0·66 (0·34-1·26)	0·20
EVG/c	1·08 (0·72-1·62)	0·70	0·66 (0·41-1·07)	0·09
DTG	1·0 (Ref)		1·0 (Ref)	
RAL	0·79 (0·51-1·23)	0·29	**0·52 (0·29-0·90)**	**0·02**

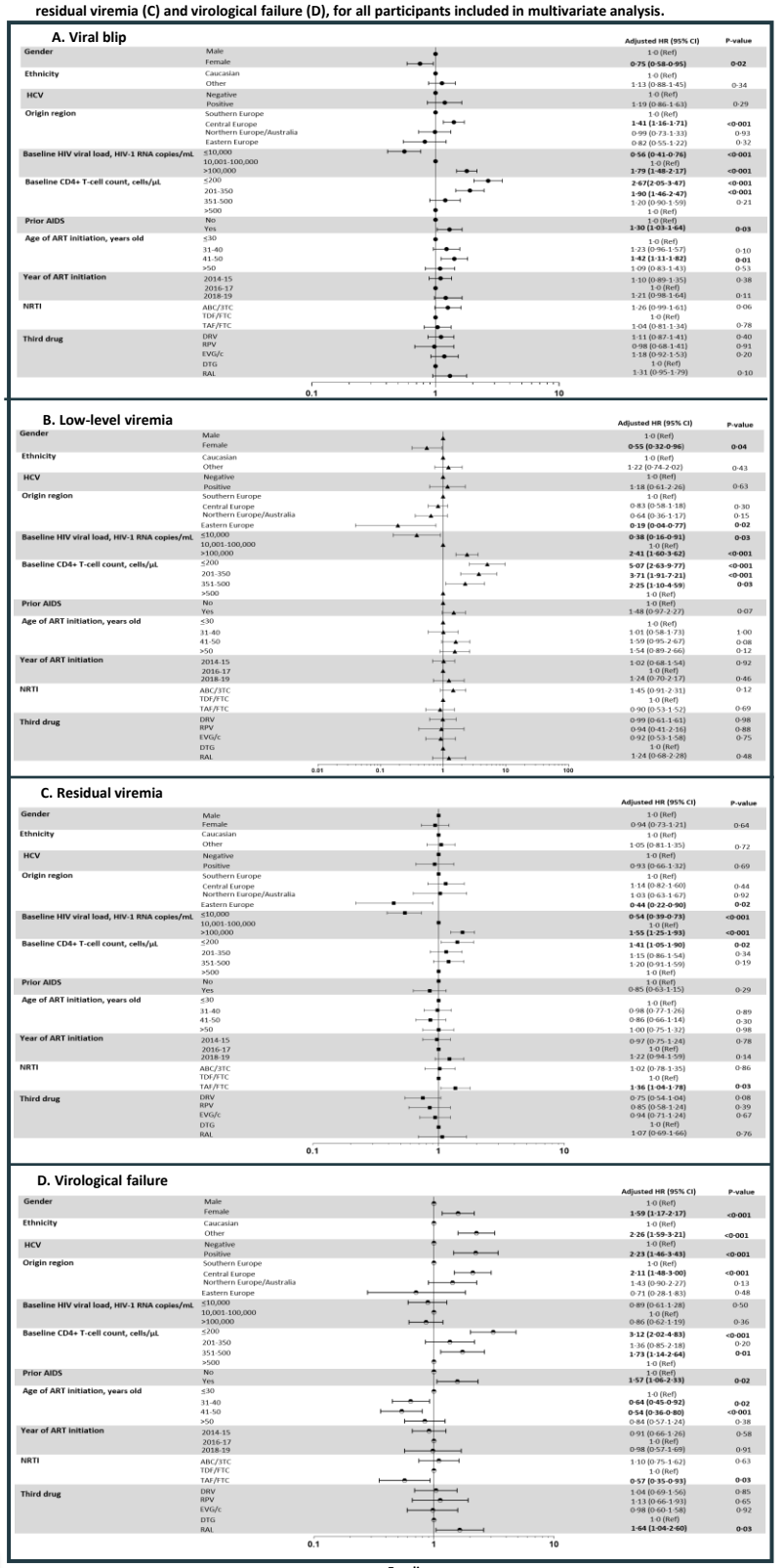
OR, odds ratio; HR, hazard ratio; CI, confidence interval; HCV, hepatitis C virus infection; AIDS, acquired immunodeficiency syndrome; NRTI, nucleos(t)ide reverse transcriptase inhibitor; ABC, abacavir; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; TAF, tenofovir alafenamide; DRV, darunavir; RPV, rilpivirine; EVG/c, elvitegravir/cobicistat; DTG, dolutegravir; RAL, raltegravir.
Statistically significant values of variables are highlighted in bold.

Table 2. Virological outcomes in the Intention-to-treat exposed population.

Virological outcome	Viral blip	Low-level viremia	Residual viremia	Virological failure	Virological suppression w48	Virological suppression w96
N included	3,750	3,750	1,493	3,914	3,638	3,118
N with outcome	600	149	475	221	3,306	2,908
% (95%CI)	9·6 (8·7-10·5)*	2·1 (1·6-2·5)*	22·2 (20·0-24·3)*	2·1 (1·7-2·6)*	91·0 (89·9-91·8)	93·3 (92·4-94·1)

N, number of participants; CI, confidence interval; *Kaplan Meier % at 12 months (95%CI)

Figure 1. Forest plots showing adjusted hazard ratio of factors associated with viral blip (A), low-level viremia (B), residual viremia (C) and virological failure (D), for all participants included in multivariate analysis.



Conclusions

- **Initial high HIV-RNA and low CD4+ count are associated with lower rates of VS at 48 and 96 weeks and higher rates of viral blips, LLV and RV. Low baseline CD4+ count is associated with higher VF rates.**
- **These associations remain with INSTI- and specifically dolutegravir-based regimens.**
- **While we cannot exclude confounding by indication, these findings suggest the impact of these baseline determinants is independent of the ART regimen initiated.**

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The RESPOND Study Group
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