HUMORAL IMMUNOGENICITY TO THIRD DOSE SARS-COV-2 mRNA VACCINE IN PEOPLE LIVING WITH HIV (PLWH) BY CURRENT CD4 COUNT AND CD4/CD8 RATIO

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BACKGROUND

Persons living with HIV (PLWH) might have an increased risk of adverse outcomes following COVID-19 and represent a priority group in vaccination programs.

COVID-19 vaccines stimulate strong antibody responses in people with HIV and CD4 counts >500/mm3, by obtaining humoral response rates comparable to those of the HIV negative population.

However, immunogenicity of vaccines is strongly related to CD4 cell count at the time of vaccination, indeed, CD4 <200/mm3 cell count significantly and independently predicts a poorer immune response to SARS-CoV-2 vaccine, placing this category as susceptible to booster doses. There is some evidence that the magnitude of SARS-CoV-2-specific T cell responses to natural infection relates to the size of the naive CD4 T cell pool and the CD4/CD8 ratio in PLWH In the era of ART, CD4:CD8 ratio might be considered as an accessible biomarker for assessing individual risks in PLWH, a proportion of whom may require tailored vaccine strategies to achieve long-term protective immunity

AIM

Aim was to investigate humoral response elicited after the third dose of SARS-CoV-2 mRNA vaccination, according to CD4 count and CD4/CD8 ratio, in a large cohort of PLWH.

METHODS

STUDY PARTICIPANTS:

PLWH of the VAXICONA-ORCHESTRA cohort who previously received a complete primary cycle of SARS-CoV-2 mRNA vaccine (3 doses) and for whom anti-S serology was available.

At the time of 3° dose vaccination participants were stratified by CD4 count

- Low CD4 count (**LCD4**)=CD4 count <200 cell/mm^3;
- Intermediate CD4 count (**ICD4**)=CD4 count 201-500 cell/mm^3;
- High CD4count (**HCD4**) =CD4 count >500 cell/mm^3

And by CD4/CD8 ratio:

- Low ratio LR: 0.0-0.59
- Intermediate ratio IR: 0.60-0.99
- High ratio HR: 1.0+

DEFINITION:

Humoral response: the immune marker IgG anti RBD value associated with a 80% Vaccine Efficacy (VE) against symptomatic infections => 506 BAU/mL (Feng et al. Nat Med. 2021)

LAB PROCEDURES:

-All values were measured with either DiaSorin, Abbott or Roche assays and standardized in BAU/mL. Abbott values were converted from AU/mL to BAU/mL using a factor of 0.142. Roche values were converted from U/mL to BAU/mL using a factor of 1.029 (Lukaszuk, K et al. Vaccines 2021, 9)

ENDPOINTS

- No response if IgG anti-RBD/S ≤ 506 BAU/mL 1 month after the 3° dose

STATISTICAL ANALYSIS

ANOVA was used to compare anti-S titres (in log2 scale); Association between CD4 groups and risk of undetectable/low level anti-S was evaluated by means of ANOVA and logistic regression all adjusted for age, VL< copies/ml and n. of comorbidities

RESULTS

General characteristics of participants by CD4 count and by CD4/CD8 ratio at the time of receiving 3° dose vaccination are shown in table 1 and 2, respectively. Proportions of responses 1 month after the 3° dose in CD4 and CD4/CD8 ratio groups are shown in Figure 1 and 2, respectively.

Table 1 –Main characteristics of target population by CD4 count at 3rd dose vaccination

Characteristics	CD4 count at 3rd dose LCDR N= 56	ICDR N= 229	HCDR N= 547	p-value*	Total N= 832
Female, n(%)	14 (25.0)	39 (17.0)	104 (19.0)	0.390	157 (18.9)
Age, years, median (IQR)	57 (53, 61)	55 (47, 61)	52 (43, 58)		54 (45, 59)
Caucasian, n(%)	41 (73.2)	183 (79.9)	492 (89.9)	<.001	716 (86.1)
BMI, median (IQR)	23 (22, 26)	24 (22, 26)	24 (22, 27)		24 (22, 27)
>=1 comorbidity, n(%)	22 (39.3)	86 (37.6)	152 (27.8)	0.011	260 (31.3)
Time from AIDS diagnosis, years, median (IQR)	5 (5, 5)	8 (7, 8)	9 (4, 13)		7 (4, 11)
Nadir CD4 count, cells/mm^3, median (IQR)	37 (11, 57)	77 (28, 155)	256 (103, 405)		164 (48, 333)
CD4 count at 3rd dose, cells/mm3, median (IQR)	138 (106, 165)	374 (296, 439)	787 (635, 992)		631 (414, 877)
HIV RNA<=50, n(%)	44 (78.6)	212 (93.0)	526 (96.5)	<.001	782 (94.3)
Vaccination times (days), Medians (IQR) From 3rd dose to response	17 (15.0, 20.0)	16 (14.0, 20.0)	16 (14.0, 17.0)	0.083	16 (14.0, 18.0)

&In those with at least one; *Chi-square or Kruskal-Wallis test as appropriate

Figure 1 –VE>=80% after 3rd dose in PLWH by CD4 count at the time of booster

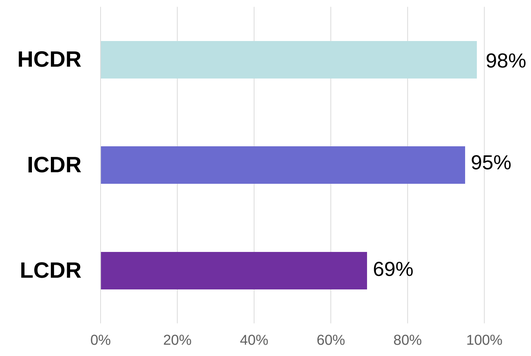
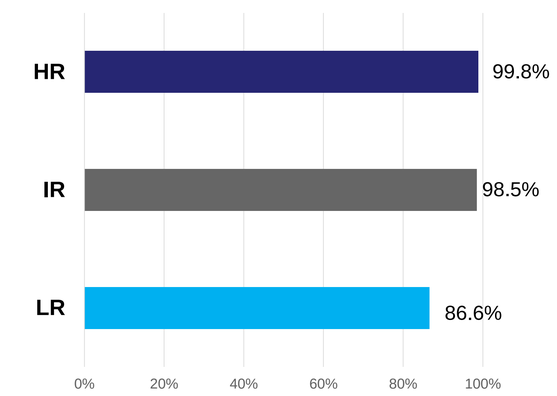


Table 2 –Main characteristics of target population by CD4/CD8 ratio at 3rd dose vaccination

Characteristics	CD4/CD8 ratio at 3rd dose LR N= 264	IR N= 200	HR N= 361	p-value*	Total N= 825
Female, n(%)	45 (17.0%)	29 (14.5%)	80 (22.2%)	0.060	154 (18.7%)
Age, years, median (IQR)	55 (47, 60)	53 (43, 58)	53 (44, 60)		54 (45, 59)
Caucasian, n(%)	212 (80.3%)	178 (89.0%)	319 (88.4%)	0.006	709 (85.9%)
BMI, median (IQR)	24 (22, 26)	24 (22, 27)	24 (22, 27)		24 (22, 27)
>=1 comorbidity, n(%)	99 (37.5%)	64 (32.0%)	92 (25.5%)	0.005	255 (30.9%)
Time from AIDS diagnosis, years, median (IQR)	5 (3, 7)	9 (7, 15)	11 (10, 15)		7 (4, 11)
Nadir CD4 count, cells/mm^3 , median (IQR)	57 (26, 154)	195 (60, 330)	281 (122, 429)		164 (48, 333)
CD4/CD8 ratio at 3rd dose, cells/mm^3, median (IQR)	0.4 (0.2, 0.5)	0.7 (0.7, 0.8)	1.3 (1.1, 1.5)		0.8 (0.5, 1.2)
HIV RNA <=50, n(%)	237 (89.8%)	187 (94.9%)	351 (97.2%)	<.001	775 (94.3%)
Vaccination times (days), Medians (IQR)					
From 3rd dose to response	16 (14.0, 18.0)	15 (14.0, 18.0)	16 (14.0, 19.0)	0.337	16 (14.0, 18.0)

&In those with at least one; *Chi-square or Kruskal-Wallis test as appropriate

Figure 2 –VE>=80% after 3rd dose in PLWH by CD4/CD8 ratio at the time of booster



aOR from fitting a logistic regression for 3rd vaccine doses responses according with CD4 count and CD4/CD8 ratio are reported in Table 3.

Table 3 –OR of non-response after 3rd dose according to CD4 count (Panel A) and to CD4/CD8 ratio (Panel B) at the time of vaccination from fitting a logistic regression analysis. CD4>500/mm3; LR, CD4/CD8 ratio 0-0.59; IR, CD4/CD8 ratio 0.60-0.99; HR, CD4/CD8 ratio >1Abbreviations: LCD4, CD4<200/mm3,ICD4, CD4 201-500/mm3, HCD4,

	Logistic regression: Fail to achieve 80% VE at 1 month after 3rd dose vaccination				
	Unadjusted Odds ratio (95% CI)	p-value	Adjusted* Odds ratio (95% CI)	p-value	&Type III p-value
Panel A					
CD4 count at time of 3rd dose					
500+	1		1		0.047
201-500	2.50 (0.58, 10.70)	0.217	2.57 (0.59, 11.17)	0.207	
0-200	21.56 (5.62, 82.77)	<.001	**23.59 (5.68, 98.02)**	**<.001**	
per 1 SD lower (log2 scale)	3.26 (2.06, 5.16)	<.001	**2.07 (1.16, 3.67)**	**0.013**	
Panel B					
CD4/CD8 ratio at time of 3rd dose					
1.00+	1		1		0.140
0.60-0.99	1.42 (0.09, 23.18)	0.804	1.49 (0.09, 24.37)	0.780	
0.00-0.59	14.53 (1.90, 111.2)	0.010	**14.02 (1.81, 108.5)**	**0.011**	
per 1 SD lower (log2 scale)	4.48 (2.56, 7.81)	<.001	**3.06 (1.49, 6.28)**	**0.002**	

*adjusted for age, VL<=50 copies/mL at time of 3rd dose and no. of comorbidities
&from the adjusted model

LIMITATIONS

- ✓Study period mainly covering alpha&delta circulating VOCs
- ✓The cut off used for 80%VE may be not valid in an epidemiological scenario dominated by Omicron
- ✓No data on waning post 3° dose here presented
- ✓No assessment of neutralizing activity

CONCLUSIONS

The 3rd dose vaccination elicited a strong humoral immune response in all the groups identified, although was lower in those with severe immunodeficiency.

Both CD4 count and CD4/CD8 ratio at time of 3rd dose are predictors of failing to achieve a 80% VE, but, when directly compared, CD4/CD8 ratio appeared to be more strongly associated. This finding is consistent with previous data on response to natural SARS-CoV-2 infection

CD4/CD8 ratio should be considered as a factor to guide future vaccination booster strategy in PLWH.

Further studies are needed to update the estimated correlates of protection from infection with currently circulating Omicron VoCs

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