Complement activation as a mechanism of protection by SARS-CoV-2 mRNA vaccine in men with HIV-1

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BACKGROUND

- People living with HIV (PLWH) are recommended to be fully vaccinated against SARS-CoV-2. However, men with HIV-1 (MWH) respond to the COVID-19 vaccine with lower immunoglobulin binding and neutralization titers against SARS-CoV-2 than men without HIV-1 (MWOH). Although neutralization is an important protective mechanism against SARS-CoV-2, other mechanisms can play a key role in protection. Therefore, we assessed antigen-specific complement activation in vaccinated MWH and MWOH.

METHODS

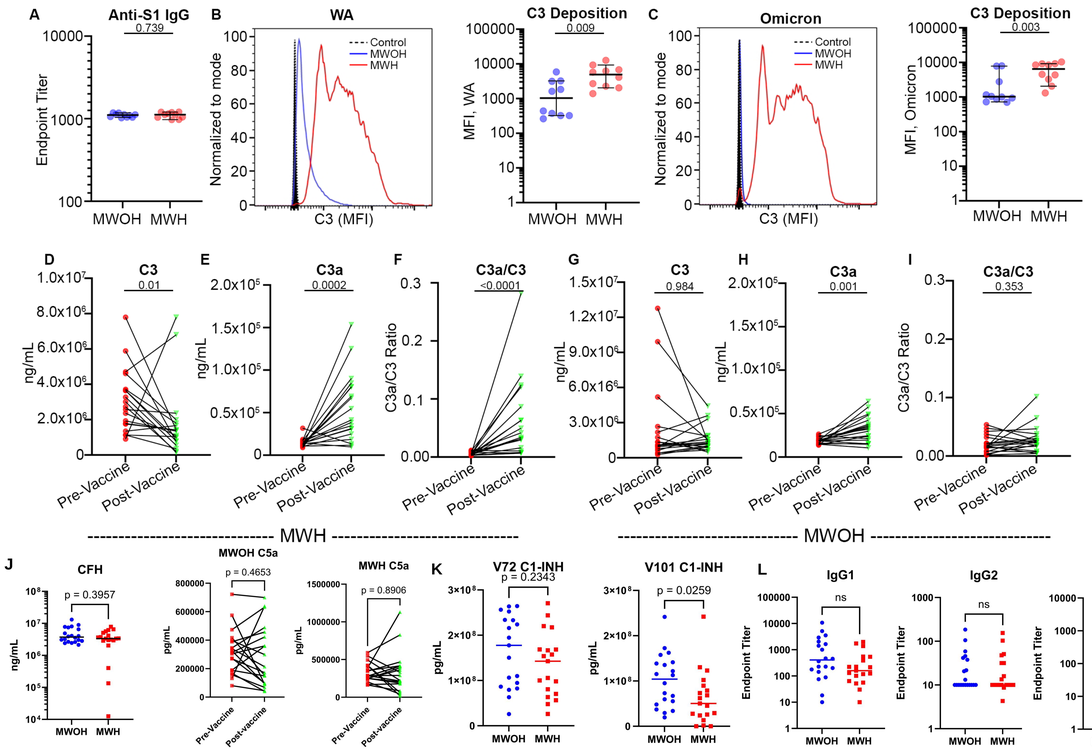
- We quantified activation of the classical compliment cascade through C3 deposition by antibodies specific for SARS-CoV-2 S1 and for the receptor binding domain (RBD) in 19 MWH and 20 MWOH from the MACS/WIHS Combined Cohort Study using a bead-based flow cytometry assay and capture C3/C3a ELISA. C5a and complement inhibitor molecules as well as IgG isotypes were quantified by ELISA. All participants were two-dose mRNA vaccinated for SARS-CoV-2 and without natural infection.

Table 1. Demographic Characteristics of MWOH and MWH in This Study

Characteristic	MWOH (n = 94)	MWH (n = 45)	*P* Value
Ethnicity			
White, non-Hispanic	76 (80.9)	36 (80.0)	NA
White, Hispanic	4 (4.26)	1 (2.22)	NA
Black, non-Hispanic	5 (5.32)	4 (8.89)	NA
Black, Hispanic	1 (1.06)	1 (2.22)	NA
Asian/Pacific Islander	1 (1.06)	0 (0.0)	NA
Unknown	7 (7.45)	3 (6.67)	NA
Clinical characteristics, median (range)			
Age, y	67 (31–84)	62 (36–86)	.345
CD4 count, cells/μL	NA	719.5 (253.0–1888)	NA
Nadir CD4 count, cells/μL	NA	669 (253–1215)	NA
Viral load, copies/mL	NA	≤20.0 (≤20.0–315)	NA
Time postvaccination, d	104 (12–249)	101 (4–253)	.704
Anti-N IgG seropositivity			.267
Anti-N IgG+	42 (44.7)	15 (33.3)	
Anti-N IgG–	52 (55.3)	30 (66.7)	
Vaccine type received			.460
mRNA-1273	42 (44.7)	16 (35.6)	
BNT-162b2	52 (55.3)	28 (62.2)	

Two doses of mRNA COVID-19 vaccine in MWH induces antibodies with ***potent complement activation*** in absence of neutralizing antibodies.

RESULTS



CONCLUSIONS

- Two doses of monovalent mRNA vaccines (BNT162-b2 and mRNA-1273) induce potent neutralizing and opsonizing antibodies against SARS-CoV-2 Washington strain in MWH. However, that vaccine induced antibodies that can induce potent complement activation when bound to Omicron antigens. In addition, MWH have lower levels of C1-IHN than MWOH whereas factor H levels are similar in both. These results suggests a predominant activation of the classical pathway. Interestingly, while MWH have higher levels of C3a/C3 than MWOH the levels of C5a/C5 are not different. Indicating that cascade is inhibited at the level of the C5 convertase.

ADDITIONAL KEY INFORMATION

- For more information of the preceding study, refer to our paper: https://doi.org/10.1093/infdis/jiad544

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- Currently ongoing investigation includes complement activation in women with HIV-1 for the University of California San Francisco MWCCS site, and antibody potency to activate NK cell killing of Infected cells.

MWCCS
MACS/WIHS COMBINED COHORT STUDY