CTN 328: Immunogenicity outcomes in people living with HIV following for COVID-19 vaccination (HIV-COV)

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Advisory boards: Viiv, Gilead

BACKGROUND

PLWH display **poor immunogenicity to common vaccines** including influenza, pneumococcal, meningococcal and Hepatitis A and B vaccines, especially with low CD 4 T cell counts (<200 cells/mm^3)/viremia

Intersecting vulnerabilities increase risk of COVID-19 acquisition and vulnerabilities

PLWH are understudied in COVID-19 vaccine clinical trials. Those enrolled often had normal CD4 T cell counts and few comorbidities→may not be generalizable to most PLWH.

OBJECTIVES

Primary: To assess immunogenicity of COVID-19 vaccination in PLWH, as assessed by COVID-19-specific IgG ELISA, at 6 months following second- dose vaccination

Secondary:

1) To assess neutralization capacity of COVID-19-specific IgG at 6 months following second-dose vaccination
2) To assess the durability of COVID-19-specific IgG response in PLWH at 12 months following third-dose vaccination
3) To assess whether COVID-19-specific IgG antibody titers and neutralization capacity differ 6-months post second vaccine dose from 6-months post third vaccine dose and whether the relationship between response at the two time points is affected by HIV status
4) To examine changes in the proportion and activation phenotype of CD4 T cells, CD8 T cells, B cells, natural killer cells and monocytes, including gene expression and cytokine production, pre- and post-vaccination
5) To determine safety and tolerability of COVID-19 vaccines in PLWH, based on local or systemic adverse events following first, second or third injections

Exploratory:

1) % of individuals with COVID-19-specific antibodies at 6 months, stratified by PLWH **subpopulations:** (e.g., low CD4 T cell counts <350 cells/mm3; obese individuals; smokers; and women

2) Ability of vaccine-elicited antibodies to cross-recognize SARS-CoV-2 S protein **variants,** including N501Y and/or E484K, using in-house assays

STUDY DESIGN

Prospective, observational cohort study involving PLWH receiving ≥1 COVID-19 vaccinations followed at 4 Canadian sites (Montreal, Ottawa, Toronto, Vancouver).

Controls from the **Stop the Spread Ottawa** (SSO) observational cohort involving over 1,000 individuals followed at similar time points

VISIT SCHEDULE

Visit number	1 (Screen)	Vaccine	2	Vaccine	3	4	5	6[1]	Vaccine	B-1[2]	B-6[2]	B-12[2]
Week Number	-12 to 0	0	4 weeks		3 mo after dose 2	6 mo after dose 2	12 mo after dose 2	15 mo after dose 2		4 weeks after dose 3	6 mo after dose 3	12 mo after dose 3
Window	-3 mo											
Inclusion/ Exclusion	X		X									
Informed Consent	X							X		X		
Medical History	X											
Blood Draw: Immunology	X		X		X	X	X	X		X	X	X
Blood Draw: CD4/Viral Load (standard of care)	X		X		X	X	X	X		X	X	X
Vaccination		X		X					X			
Participant Diary		X	X	X	X				X	X		
CITF Questionnaire	X		X		X	X	X	X		X	X	X
Adverse Events			X		X					X		
Concomitant Meds	X		X		X	X	X	X		X	X	X

[1]Additional visit for participants who do not receive a third COVID-19 vaccine dose.
[2]Additional visits for participants receiving a third COVID-19 vaccine dose.

DATA SOURCES

Medical and HIV history
Medications, antiretrovirals
CD4, CD4/CD8 ratio, nadir CD4
Tobacco and cannabis use
Hx of COVID-19 infection

COVID-19 CITF
Standardized Core Survey
Data Element

Safety and Tolerability of COVID-19 Vaccines in PLWH: Symptoms Diary

Local reactions: redness, pain or swelling at injection site (7 and 30 days post injection)

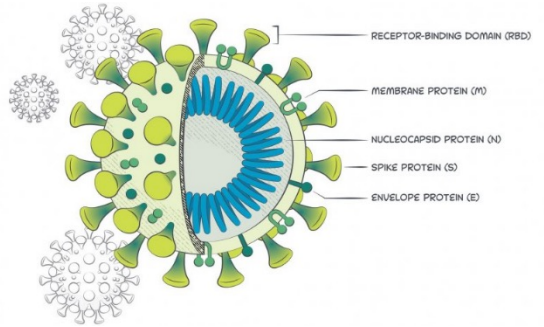
Systemic reactions: (fatigue, headache, muscle pain, fever, joint pain, diarrhea (7 and 30 post injection)

Breakthrough infections 14+ days post vaccination:
Participants complete COVID-19 Symptoms Questionnaire Survey and receive by mail courier 6 saliva kits (DNA Genotek OM 505). Participants collect saliva specimens upon receipt of the saliva kits, followed by day 7, 14, 21, 30 and 60 days post symptom onset and return via post.

HUMORAL IMMUNE STUDIES

Antibody titers: levels of IgM, IgA and IgG vs. SARS-CoV-2 S protein receptor binding domain (RBD) and nucleocapsid protein **distinguishing vaccine-induced (S only) from infection-induced (S and N) responses**

IgM and IgG antibody **cross-recognition of RBD of variants of concern (VOCs)**→ Assay can be rapidly adapted to accommodate emerging VOCs



Neutralization Assays: Capacity to **block viral entry**
→Retroviruses pseudotyped with SARS-CoV-2 S protein

T-CELL MEDIATED IMMUNE STUDIES

Phenotyping of CD4 and CD8 T cells and subset, B cells, natural killer cells and monocytes
Cytokine profiling and markers of gut microbial translocation
COVID-19 specific T cell responses
Single-cell RNA sequencing of PBMCs

ANALYSIS PLAN:

Regression techniques will be used to compare COVID-19-specific immune responses between

A) ”unstable” HIV+ group and “stable” (“reference”) HIV+ group
B) HIV+ group and HIV- group

Will control for factors believed to be associated with immune response.
Unadjusted analyses will reveal whether there are differences driving factors associated with group membership

DATA REPORTING

We will stratify results by:
-number of doses received
-time interval between the two doses
-sex
-individuals who are naïve to COVID-19 vs those with pre- existing antibodies

We will report data from exploratory analyses descriptive statistics and data for vaccines from different manufacturers separately and combined

RESULTS

	Total participants recruited N=375
Sex	
Males	275
Females	94
Vaccines at enrolment	
None	98
1	143
2	134
Subpopulation	
Age >55 years	165
CD4 T cell counts <350 cells/mm^3	28
Multimorbidity	126
"Stable" or "reference" group	146

VISIT TRACKER

Site	Visit 1	Visit 2 + Visit 1/2	Visit 3 + Visit 1/3	Visit 4	B1	B6	Withdrawals
	Pre-vaccine	4 Wks after dose 1	3 Mths after dose 2	6 Mths after dose 2	4 Wks after dose 3	6 Mths after dose 3	
Montreal	14	28	100	79	51	3	4
Ottawa	14	96	79	32	54	1	8
Toronto	4	12	62	51	13	0	3
Vancouver	66	97	96	62	85	0	9
Study Total	**98**	**233**	**337**	**224**	**203**	**4**	**24**

IMMUNOGENICITY STUDIES

All serum collected to date will undergo humoral immunity testing in May 2022.

Optimization experiments for T-cell mediated immunity completed. Analyses will commence on participant specimens in May 2022.

RELEVANCE

Findings will be shared with CITF, National Advisory Committee on Immunization, community, and other stakeholders

End goal to inform clinical practice guidelines related to COVID-19 vaccination in PLWH in order to reduce COVID-19 related morbidity and mortality.

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COVID-19 IMMUNITY TASK FORCE