NASEM Workshop:
Toward A Common Research Agenda
in Infection-Associated Chronic Illnesses

Common Ground:
Microbial Persistence, Immune Dysregulation and Inflammation Following SARS-CoV-2 and other Infection-Associated Chronic Illnesses

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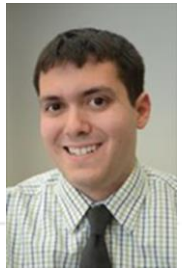
UCSF University of California San Francisco

LIINC Long-term Impact of Infection with Novel Coronavirus

POLYBIO

UCSF Long-Term Immunological Impact of Novel Coronavirus Study (LIINC) study was launched early in the pandemic



Reports of post-acute symptoms in hospitalized and non-hospitalized patients emerged early in the pandemic

The emerging long-term complications of Covid-19, explained

"It is a true roller coaster of symptoms and severities, with each new day offering many unknowns."

By Lois Parshley | May 8, 2020, 1:10pm EDT

From 'brain fog' to heart damage, COVID-19's lingering problems alarm scientists

By Jennifer Couzin-Frankel | Jul. 31, 2020 , 1:30 PM

Surviving Covid-19 May Not Feel Like Recovery for Some

Debilitating symptoms can last long after a person's body has gotten rid of the coronavirus, a reality Italians are now confronting.

PRESS PLAY WITH MADELEINE BRAND

Think COVID-19 lasts 2 weeks? This patient has been suffering for months

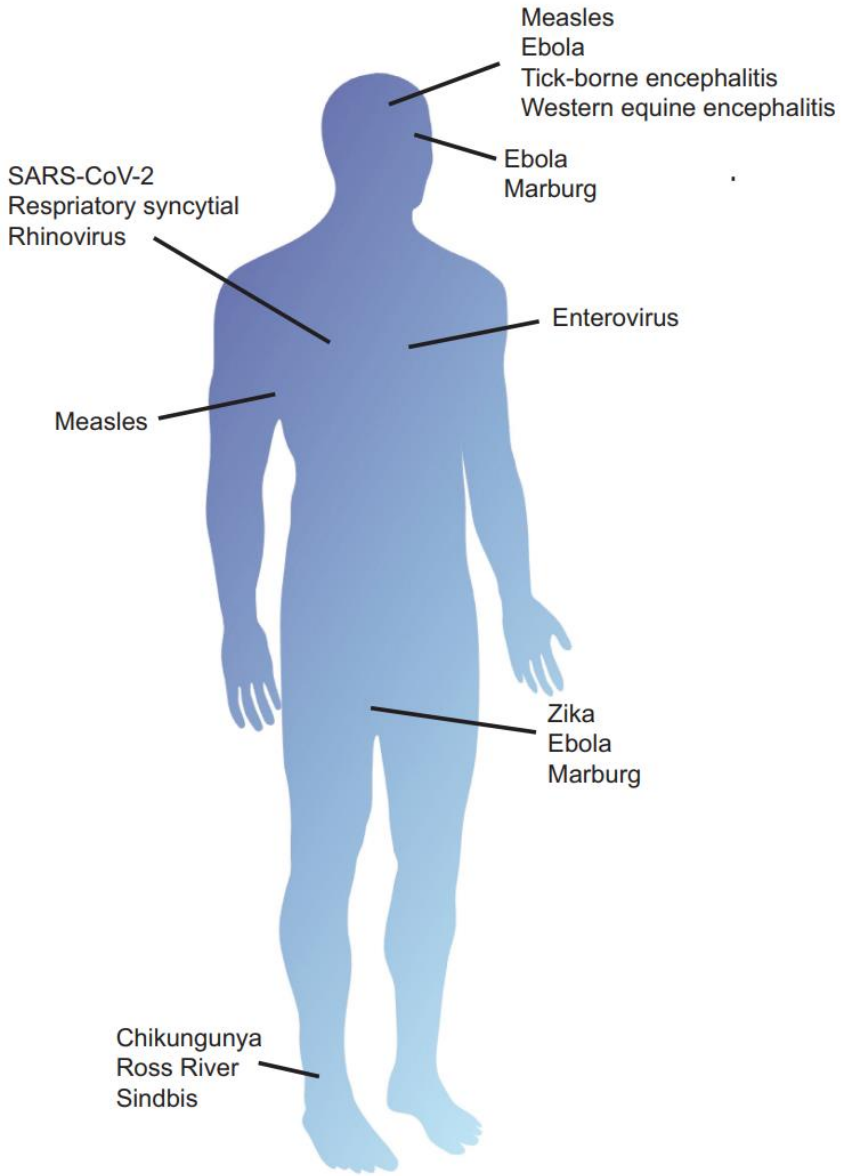
Hosted by Madeleine Brand • Jul. 24, 2020 CORONAVIRUS

Overview

- Long COVID/PASC – SARS-CoV-2 is not the only cause of infection-associated chronic illnesses
- Various “acute” viral infections lead to chronic sequelae – with or without viral persistence over time
- Chronic viral infections (e.g. HIV-1, EBV) may be a model for, or contributor to, infection-associated chronic illnesses
- Potential mechanisms of infection-associated chronic illnesses, including Long COVID
- Other non-viral infection-associated chronic illnesses

LC is Not Alone: RNA Virus Infection & Long-Term Implications

Virus	Sites of RNA persistence	Cell type	Consequences
Picornavirus			
Rhinovirus	Respiratory tract	Epithelial cells?	Asthma
Enterovirus	Heart	Cardiac myocytes	Cardiomyopathy
Hepatitis A	Liver	Hepatocytes	Late hepatitis relapse
Polio	Brain and spinal cord	Motor neurons	Late progression of paralysis and fatigue
Alphavirus			
Chikungunya	Joints	Macrophages	Persistent joint pain
Ross River	Joints	Macrophages	Persistent joint pain
Sindbis	Joints	Macrophages?	Persistent joint pain
Flavivirus			
Zika	Testes	Sertoli cells	Late sexual transmission
Japanese encephalitis	Brain	Neurons	Encephalitis relapse and Parkinson-like disease
West Nile	Kidney?	Unknown	Kidney failure?
Tick-borne encephalitis	Brain	Neurons	Late progressive encephalitis
Coronavirus			
SARS-CoV-2	Respiratory tract and intestine	Epithelial cells and macrophages?	Long COVID/PASC?
Arenavirus			
Lassa	Testes, kidney, and respiratory tract	Sertoli cells?	Epididymitis
Paramyxovirus			
Measles	Lymphoid tissue and brain	Lymphocytes, monocytes, and neurons	Life-long immunity; late progressive CNS disease (SSPE)
Respiratory syncytial	Respiratory tract	Epithelial cells and macrophages?	Chronic pulmonary disease
Filovirus			
Ebola	Testes, eye, and brain	Endothelial cells and macrophages	Late sexual transmission; recurrent/progressive uveitis and encephalitis; postviral syndrome
Marburg	Testes	Sertoli cells	Late sexual transmission



Griffin, PLoS Biology 2022

Acute Viral Infections (e.g. Ebola) Can Lead to Persistent Symptoms and Inflammation

CENTERS FOR DISEASE CONTROL AND PREVENTION

- **Tiredness**
- **Headaches**
- **Muscle and joint pain**
- **Eye and vision problems**
- **Weight gain**
- **Stomach pain or loss of appetite**

https://www.cdc.gov/vhf/ebola/treatment/survivors.html

nature COMMUNICATIONS

Long-lasting severe immune dysfunction in Ebola virus disease survivors

Aurélie Wiedemann[1], Emile Foucat[1], Hakim Hocini[1], Cécile Lefebvre[1], Boris P. Hejblum[2], Mélany Durand[2], Miriam Krüger[2], Alpha Kabinet Keita[3,4], Ahidjo Ayouba[3], Stéphane Mély[5], José-Carlos Fernandez[1], Abdoulaye Touré[3,4,6], Slim Fourati[7], Claire Lévy-Marchal[8], Hervé Raoul[5], Eric Delaporte[3], Lamine Koivogui[6], Rodolphe Thiébaut[2,9], Christine Lacabaratz[1,11], Yves Lévy[1,10,11]✉ & PostEboGui Study Group*

Median 23 months following discharge:

Increased of blood markers of inflammation, intestinal tissue damage, T cell and B cell activation and exhaustion

Ebola Can Lead to Persistent Infection in Immune Privileged Sites

THE LANCET

Late Ebola virus relapse causing meningoencephalitis: a case report

Michael Jacobs, Alison Rodger, David J Bell, Sanjay Bhagani, Ian Cropley, Ana Filipe, Robert J Gifford, Susan Hopkins, Joseph Hughes, Farrah Jabeen, Ingolfur Johannessen, Drosos Karageorgopoulos, Angie Lackenby, Rebecca Lester, Rebecca S N Liu, Alisdair MacConnachie, Tabitha Mahungu, Daniel Martin, Neal Marshall, Stephen Mepham, Richard Orton, Massimo Palmarini, Monika Patel, Colin Perry, S Erica Peters, Duncan Porter, David Ritchie, Neil D Ritchie, R Andrew Seaton, Vattipally B Sreenu, Kate Templeton, Simon Warren, Gavin S Wilkie, Maria Zambon, Robin Gopal, Emma C Thomson

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Persistence of Ebola Virus in Ocular Fluid during Convalescence

Jay B. Varkey, M.D., Jessica G. Shantha, M.D., Ian Crozier, M.D., Colleen S. Kraft, M.D., G. Marshall Lyon, M.D., Aneesh K. Mehta, M.D., Gokul Kumar, M.D., Justine R. Smith, M.B., B.S., Ph.D., Markus H. Kainulainen, Ph.D., Shannon Whitmer, Ph.D., Ute Ströher, Ph.D., Timothy M. Uyeki, M.D., M.P.H., M.P.P., Bruce S. Ribner, M.D., M.P.H., and Steven Yeh, M.D.

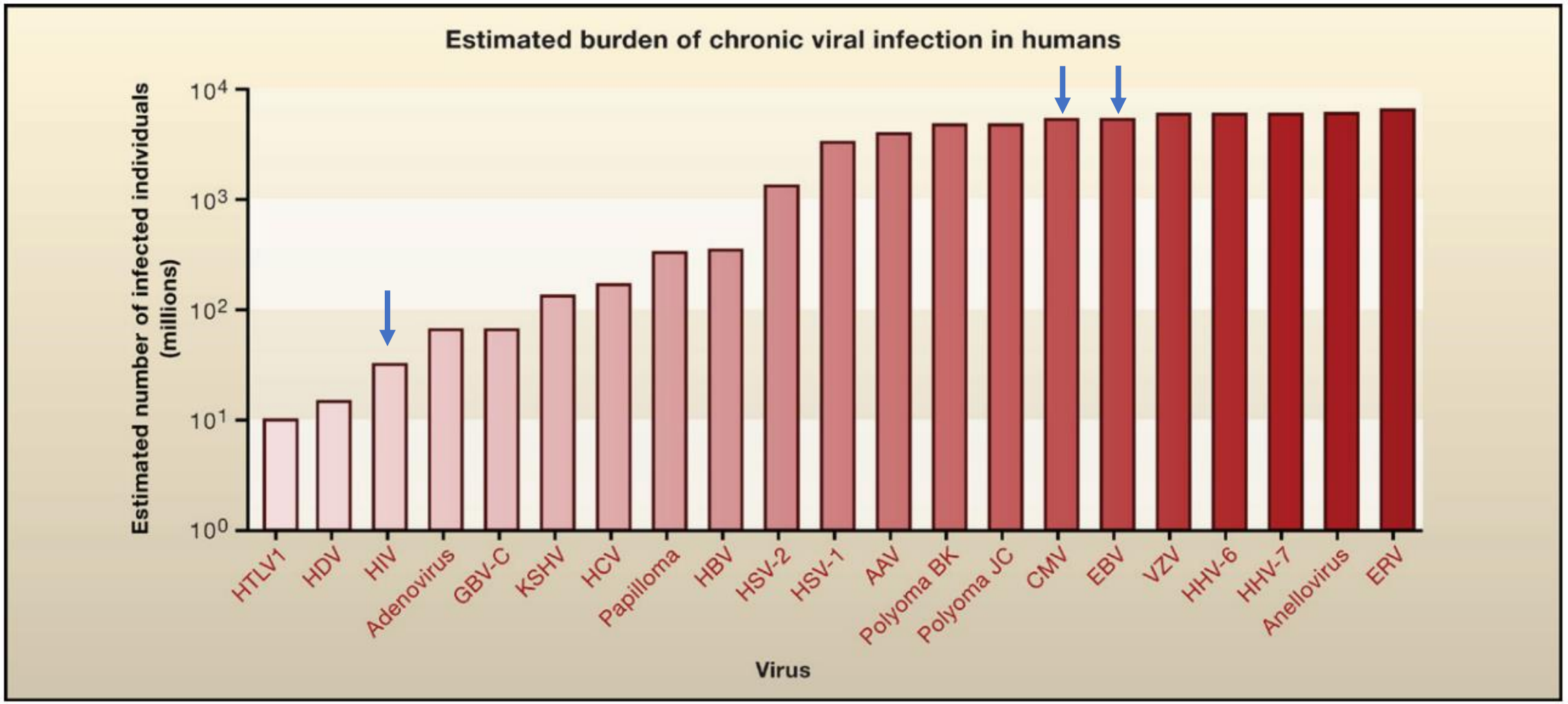
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Ebola Virus Transmission Initiated by Relapse of Systemic Ebola Virus Disease

P. Mbala-Kingebeni, C. Pratt, M. Mutafali-Ruffin, M.G. Pauthner, F. Bile, A. Nkuba-Ndaye, A. Black, E. Kinganda-Lusamaki, M. Faye, A. Aziza, M.M. Diagne, D. Mukadi, B. White, J. Hadfield, K. Gangavarapu, N. Bisento, D. Kazadi, B. Nsunda, M. Akonga, O. Tshiani, J. Misasi, A. Ploquin, V. Epaso, E. Sana-Paka, Y.T.T. N'kasar, F. Mambu, F. Edidi, M. Matondo, J. Bula Bula, B. Diallo, M. Keita, M.R.D. Belizaire, I.S. Fall, A. Yam, S. Mulangu, A.W. Rimion, E. Salfati, A. Torkamani, M.A. Suchard, I. Crozier, L. Hensley, A. Rambaut, O. Faye, A. Sall, N.J. Sullivan, T. Bedford, K.G. Andersen, M.R. Wiley, S. Ahuka-Mundeke, and J.-J. Muyembe Tamfum

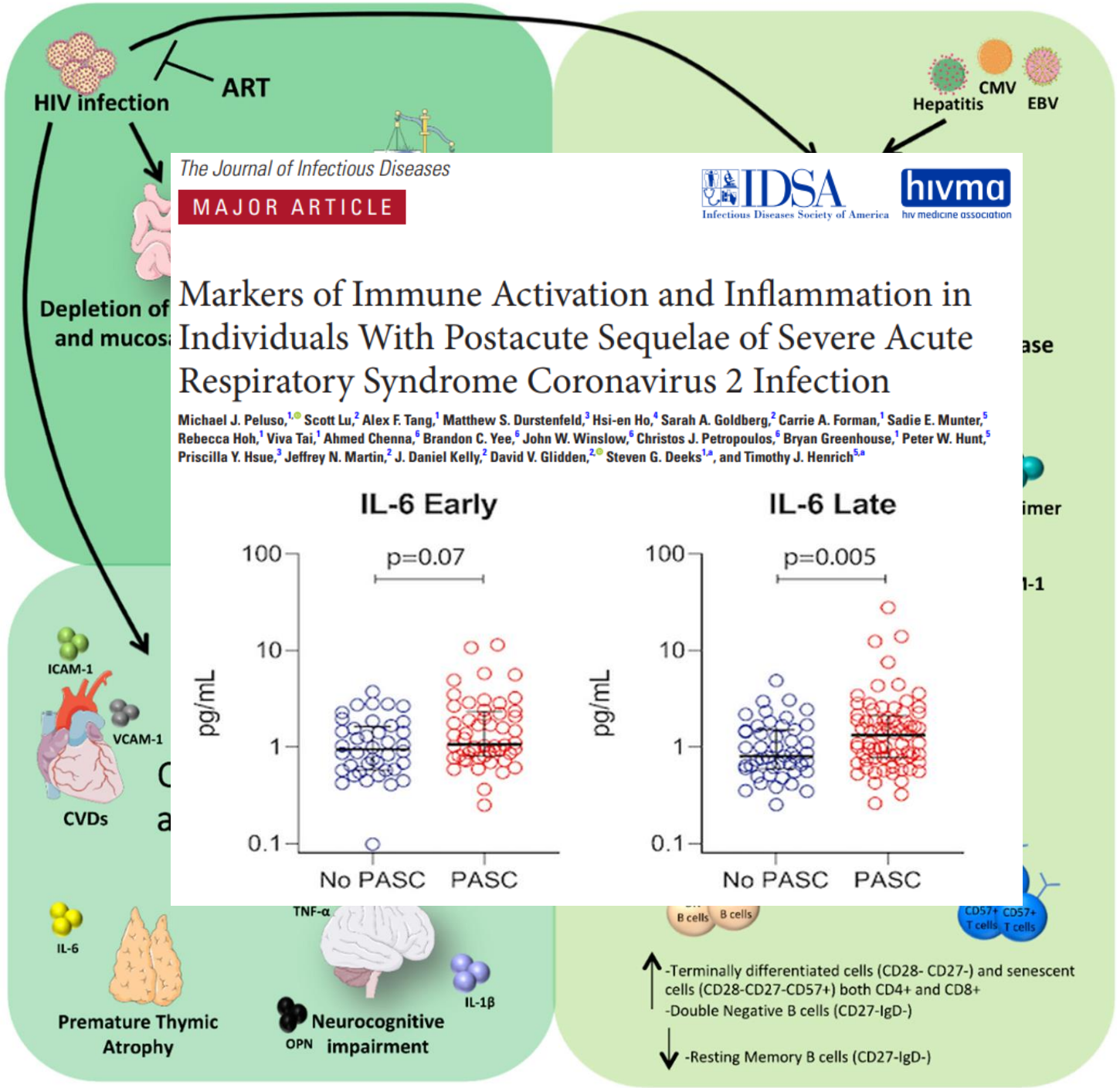
Large Burden of Acute and Chronic Viral Infections World-Wide



Virgin, Wherry, Ahmed; Cell 2009

Persistent HIV-1 Leads to Aberrant Immune Responses, Inflammation and Organ Damage Despite Antiviral Therapy

HIV-1 RNA and protein expression persists despite suppressive ART



The Journal of Infectious Diseases
MAJOR ARTICLE
IDSA Infectious Diseases Society of America
hivma hiv medicine association

Markers of Immune Activation and Inflammation in Individuals With Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection

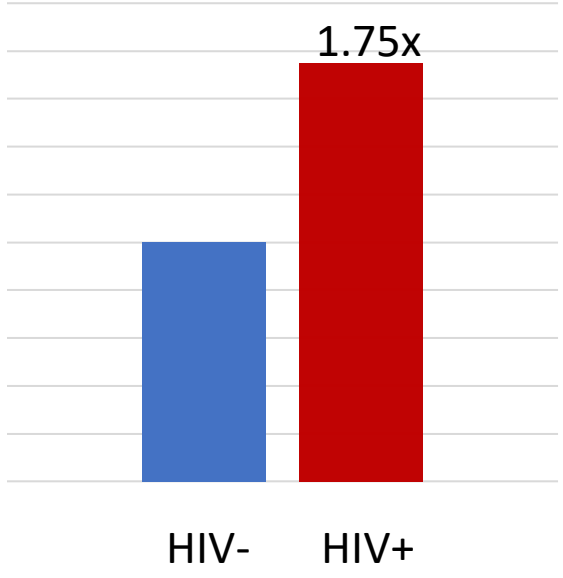
Michael J. Peluso,[1] Scott Lu,[2] Alex F. Tang,[1] Matthew S. Durstenfeld,[3] Hsi-en Ho,[4] Sarah A. Goldberg,[2] Carrie A. Forman,[1] Sadie E. Munter,[5] Rebecca Hoh,[1] Viva Tai,[1] Ahmed Chenna,[6] Brandon C. Yee,[6] John W. Winslow,[6] Christos J. Petropoulos,[6] Bryan Greenhouse,[1] Peter W. Hunt,[5] Priscilla Y. Hsue,[3] Jeffrey N. Martin,[2] J. Daniel Kelly,[2] David V. Glidden,[2] Steven G. Deeks[1,a], and Timothy J. Henrich[5,a]

Zicari et al. Viruses2019

HIV-1 and SARS-CoV-2: Insult on Injury?

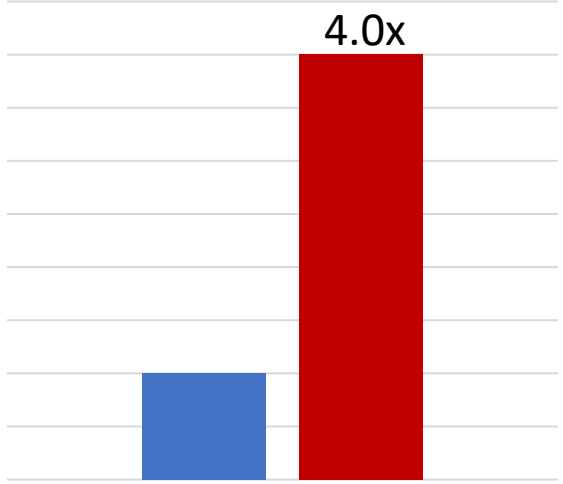
Health Status, Persistent Symptoms, and Effort Intolerance One Year After Acute COVID-19 Infection

- **PWH 1.75x as likely to have Long COVID** compared to HIV-negative
- Only 10 PWH in cohort of 530 participants



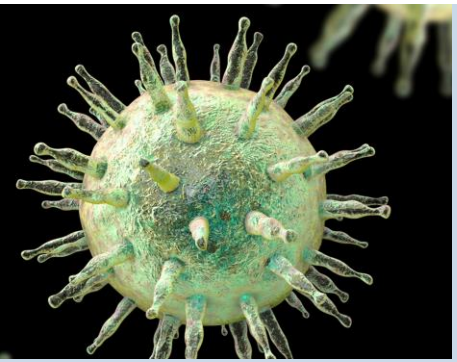
POST-ACUTE SEQUELAE AND ADAPTIVE IMMUNE RESPONSES IN PEOPLE LIVING WITH HIV RECOVERING FROM SARS-COV-2 INFECTION

- Case-control study of ~40 PWH and matched controls
- **PWH 4x as likely to have Long COVID** compared to HIV-negative



LIINC

EBV Infection is Inflammatory and Can Lead to Persistent Symptoms



- Sx persist for many weeks (up to 6 months in some individuals)
- Fatigue can be profound
- Risk of HLH/MAS
- EBV has latent and lytic stages & express immune evasion proteins
- Autoreactivity

EBV and Post-Viral Sequelae – The MS Connection?

Science

Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis

- Prospective study of 10 million military recruits, 955 diagnosed with MS during study
- Risk of MS increased 32-fold after EBV infection but not after infection with CMV
- NF-L levels went up following EBV infection (neuronal injury)

Bjornevik et al., 2022

Viewpoint Open Access | 10.1172/JCI164141

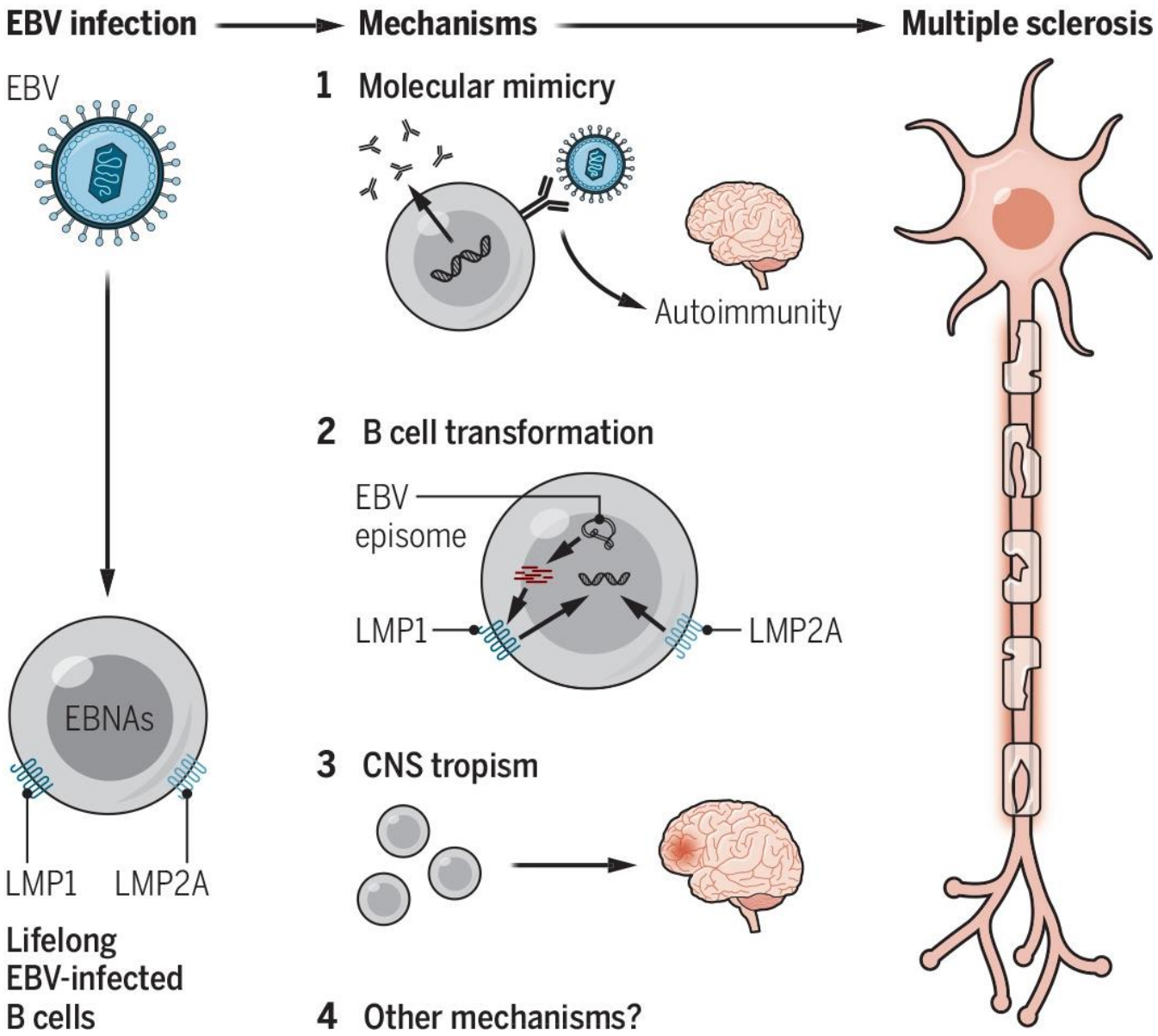
Falling down the biological rabbit hole: Epstein-Barr virus, biography, and multiple sclerosis

Ralph I. Horwitz,[1] Allison Hayes-Conroy,[2] Burton H. Singer,[3] Mark R. Cullen,[4] Kimberly Badal,[5] and Ida Sim[6]

Published September 1, 2022 - More info

EBV and Potential Mechanisms of MS

- In MS, B cells gain access to CNS through the blood-brain barrier (BBB)
- Synthesis of immunoglobulins by clonal expansions of plasmablasts within the brain causes oligoclonal immunoglobulin bands
- Cross Reactivity between EBNA1 and glial cell adhesion molecule (GlialCAM) (Lanz et al. 2022)



Robinson & Steinman, Science 2022

Human Herpesvirus Reactivation in COVID-19

pathogens

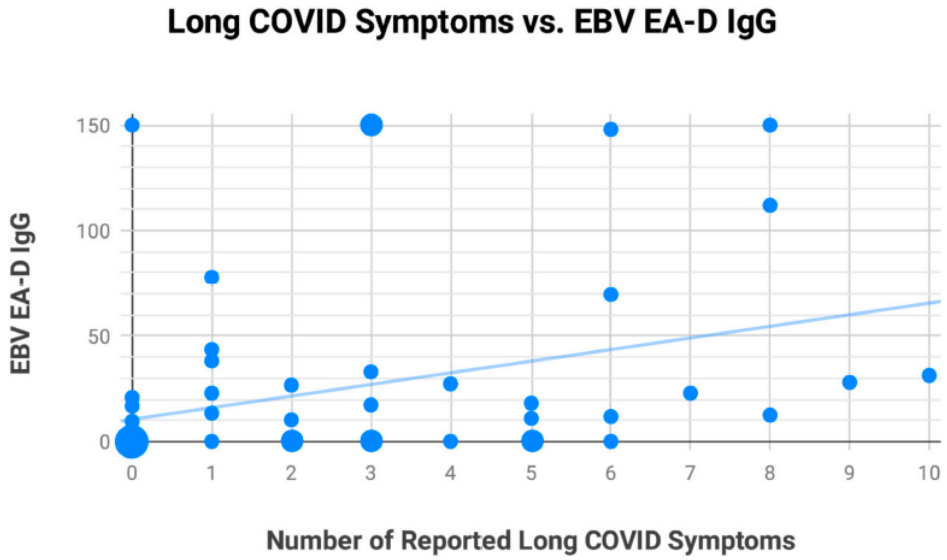
Investigation of Long COVID Prevalence and Its Relationship to Epstein-Barr Virus Reactivation

67% of people with Long COVID (vs 10% of those with full recovery) had evidence of EBV reactivation (early antigen diffuse IgG titers)

Cell

Multiple early factors anticipate post-acute COVID-19 sequelae

Found EBV viremia in early recovery predicted certain persistent symptoms 2-3 months later



Does EBV Reactivation During Acute COVID-19 Lead to Long-Term Sequelae?

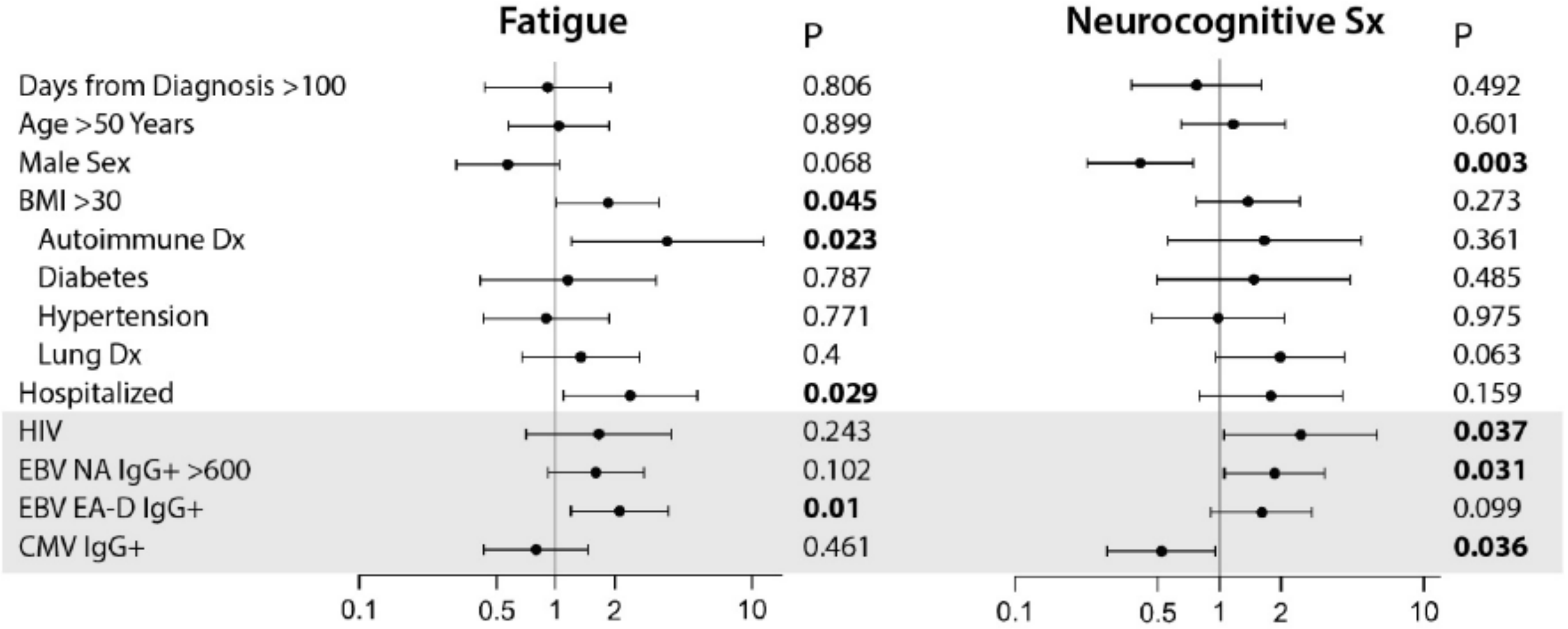
(Gold et al. 2021; Su et al. 2022)

EBV EA-D IgG and EBNA IgG Associated with Fatigue and Neurocognitive LC

JCI The Journal of Clinical Investigation

Chronic viral coinfections differentially affect the likelihood of developing long COVID

Michael J. Peluso, … , Peter W. Hunt, Timothy J. Henrich



ANNALS of Clinical and Translational Neurology
Open Access
AMERICAN NEUROLOGICAL ASSOCIATION

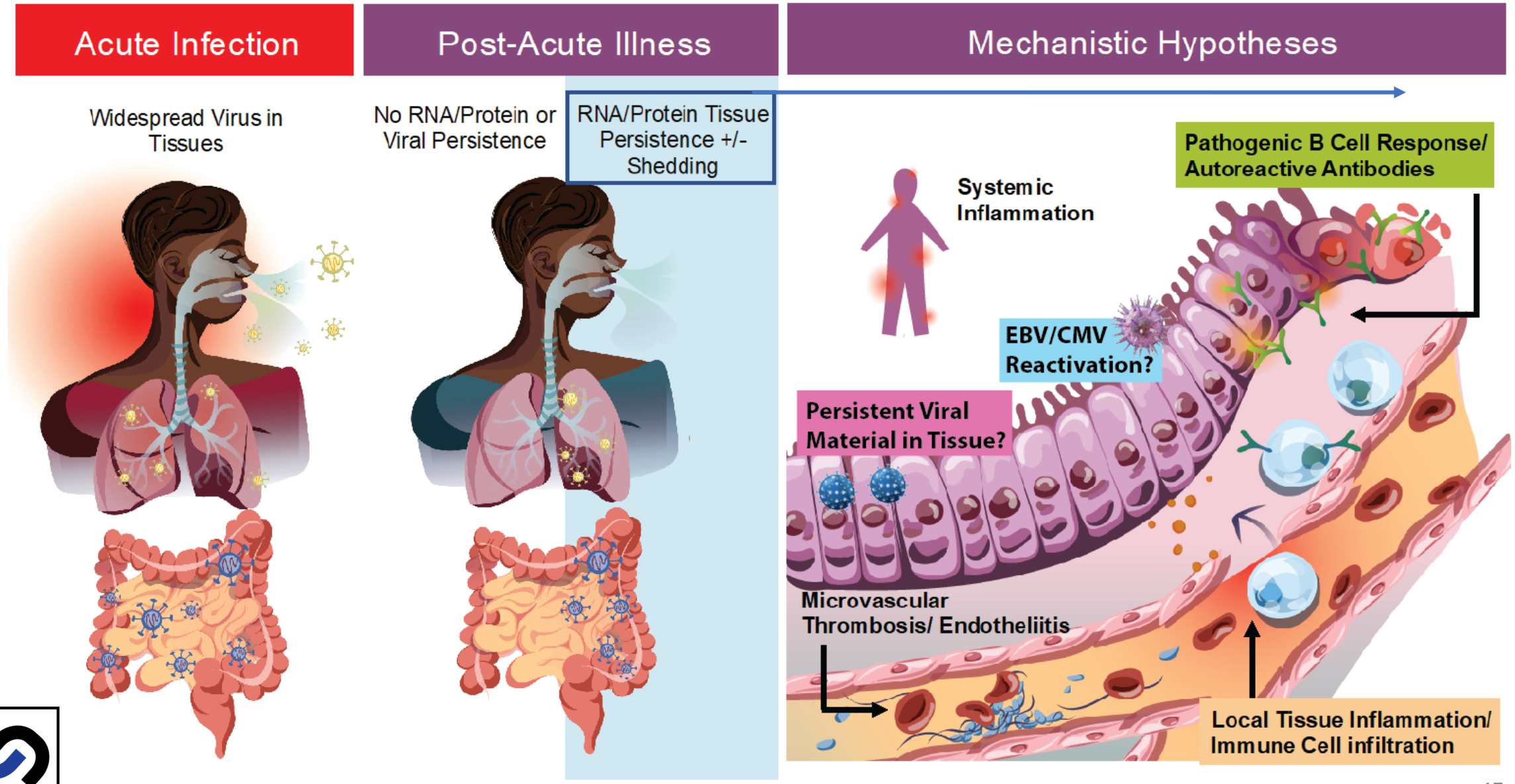
Brief Communication | Open Access

Risk factors and abnormal cerebrospinal fluid associate with cognitive symptoms after mild COVID-19

Alexandra C. Apple, Alexis Oddi, Michael J. Peluso, Breton M. Asken, Timothy J. Henrich, J. Daniel Kelly, Samuel J. Pleasure, Steven G. Deeks, Isabel Elaine Allen, Jeffrey N. Martin, Lishomwa C. Ndhlovu, Bruce L. Miller, Melanie L. Stephens, Joanna Hellmuth ... See fewer authors

- Values for CSF white blood cells, glucose, calculated CSF/serum albumin ratio, IgG index, CSF IgG level, and serum IgG level did not differ between participant groups
- Abnormal **oligoclonal banding (OCB)** patterns were identified in **69% (9/13)** of participants with cognitive PASC compared to **0% of cognitive controls** ($p = 0.03$)

Potential Mechanisms of PASC / Long COVID

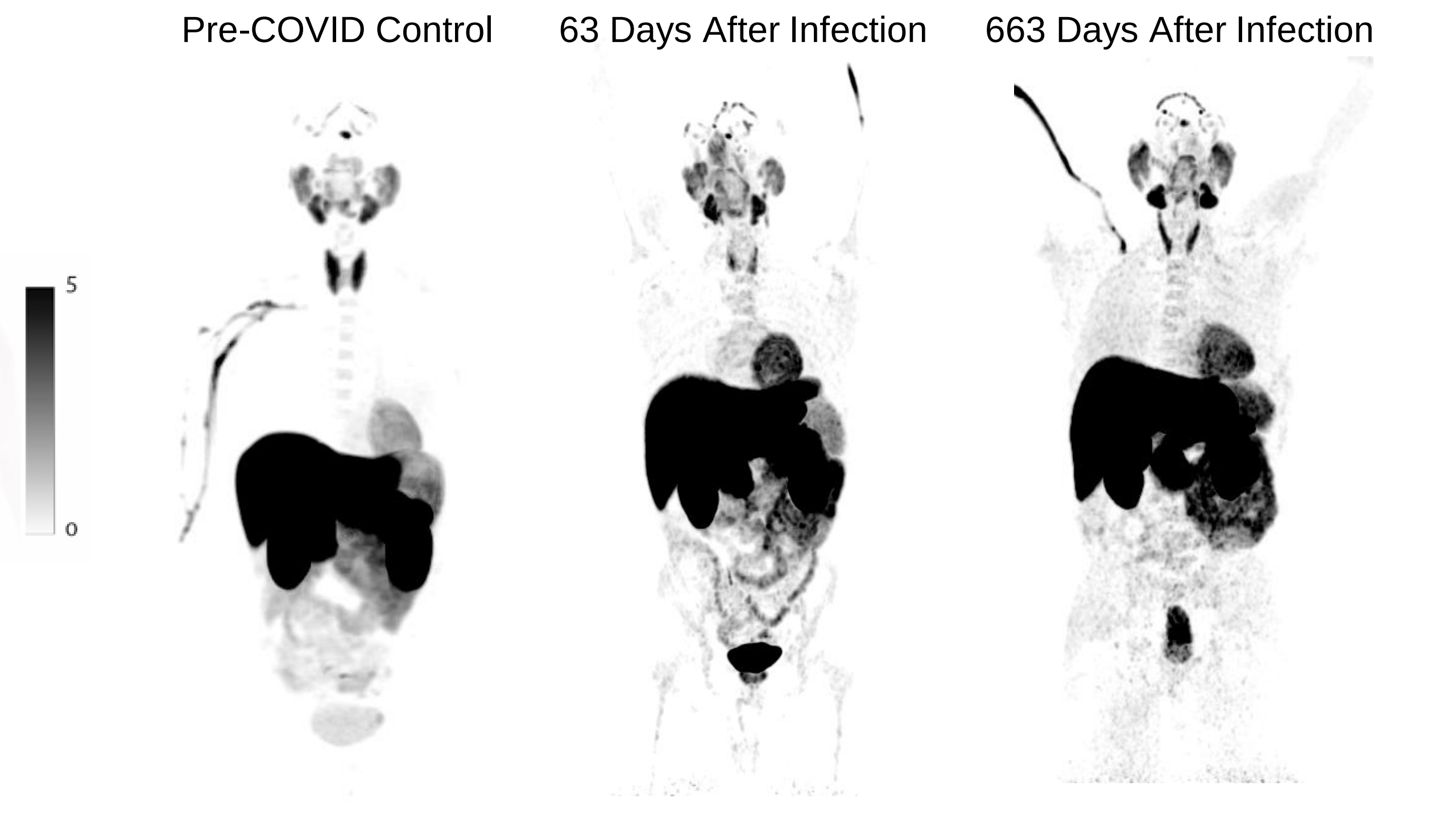


LIINC

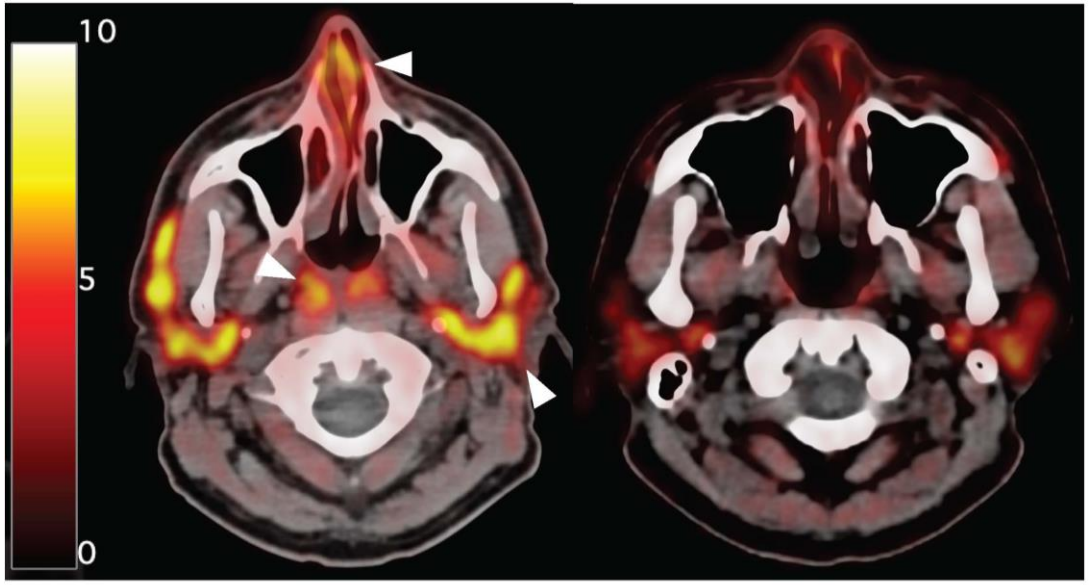
Artwork: Shirley Shao, UCSF MS2

Duration of Immune Perturbation and Inflammation in LC

- ^{18}F-AraG PET-CT Imaging in Long COVID – specific marker of activated T cells following antigen exposure (Levi et al. 2022)
- 24 participants, each with prior COVID-19 infection
- 27 to 910 days (2.5 years) out from infection (median 195 days)
- Up to 15 LC symptoms reported (median 6 symptoms)
- 6 reported no LC symptoms

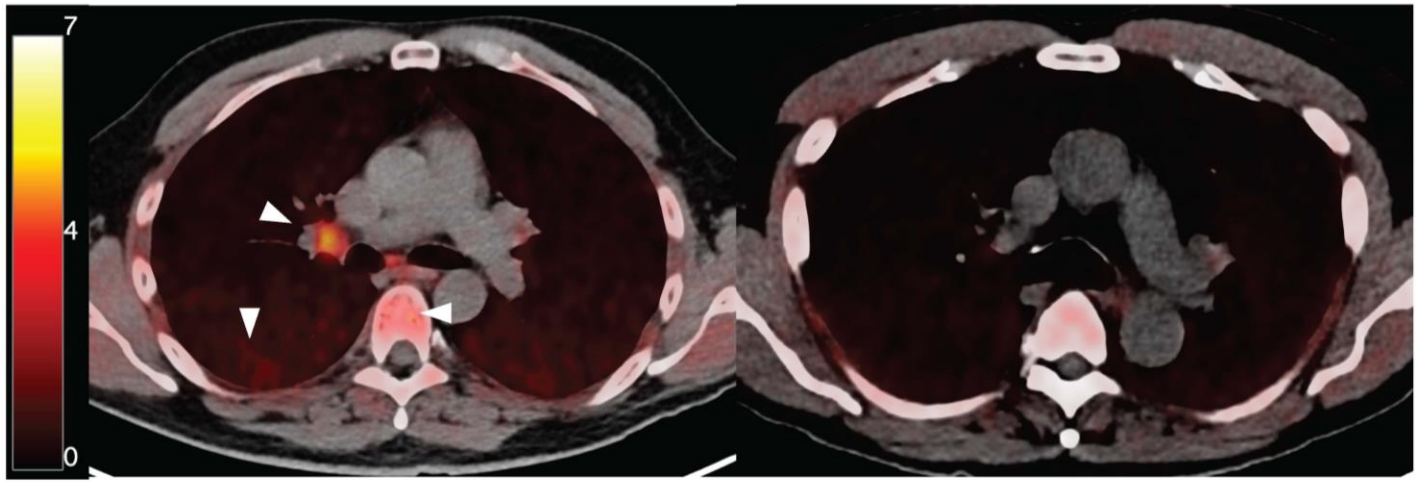

Pre-COVID Control
63 Days After Infection
663 Days After Infection
5
0

Increased T Cell Activation In Many Tissues Years Post-COVID-19 Compared to Pre-COVID Controls



Pt 13: 246 Days Post-COVID

Control 7

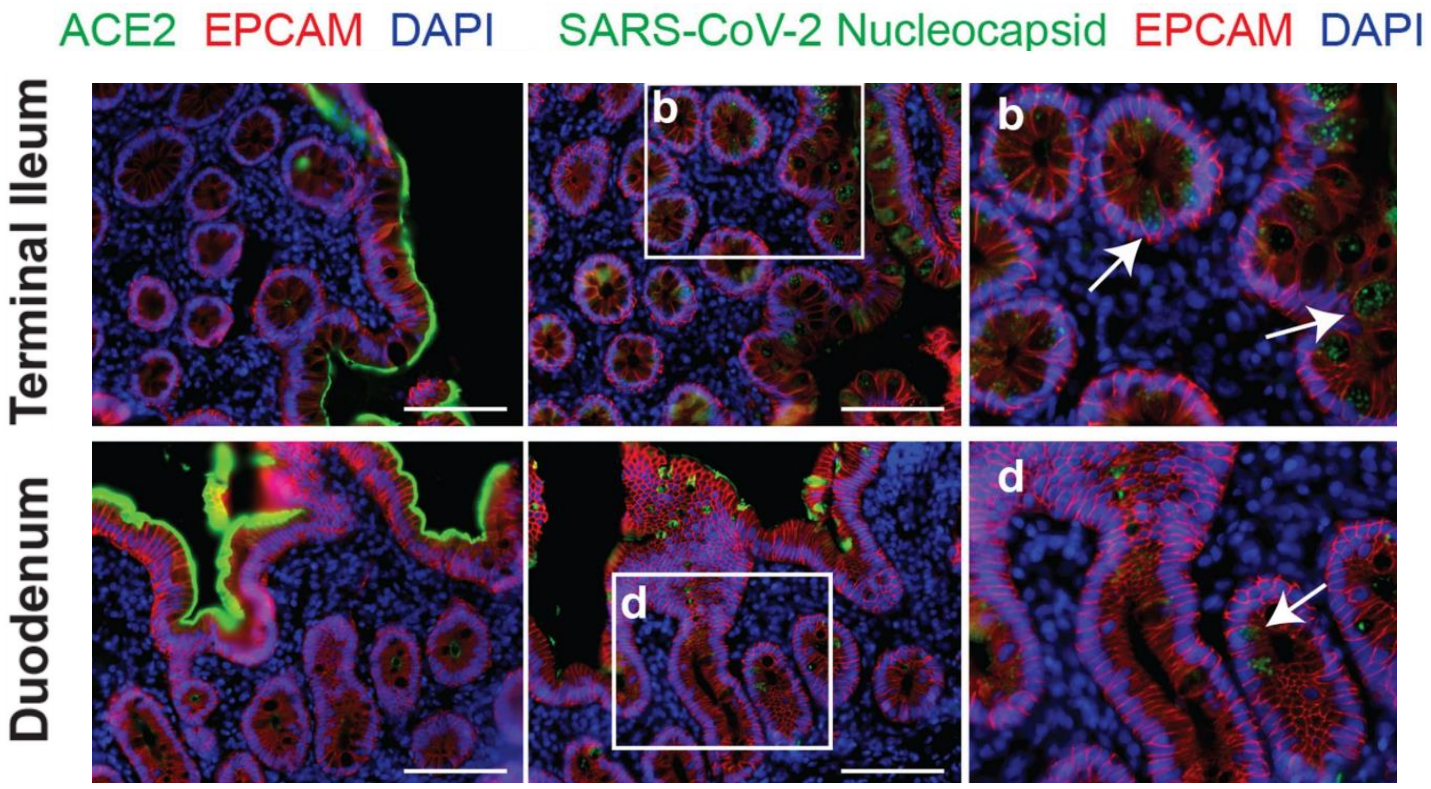


Pt 16: 625 Days Post-COVID

Control 7

Increased tracer uptake in nasopharyngeal tissues, bone marrow, hilar lymph nodes, lung parenchyma, colon/rectal wall, **brain stem**, pulmonary vasculature and **spinal cord** in post-COVID pts compared with pre-COVID controls

SARS-CoV-2 protein persists in gut tissue up to 6 months post-infection



nature

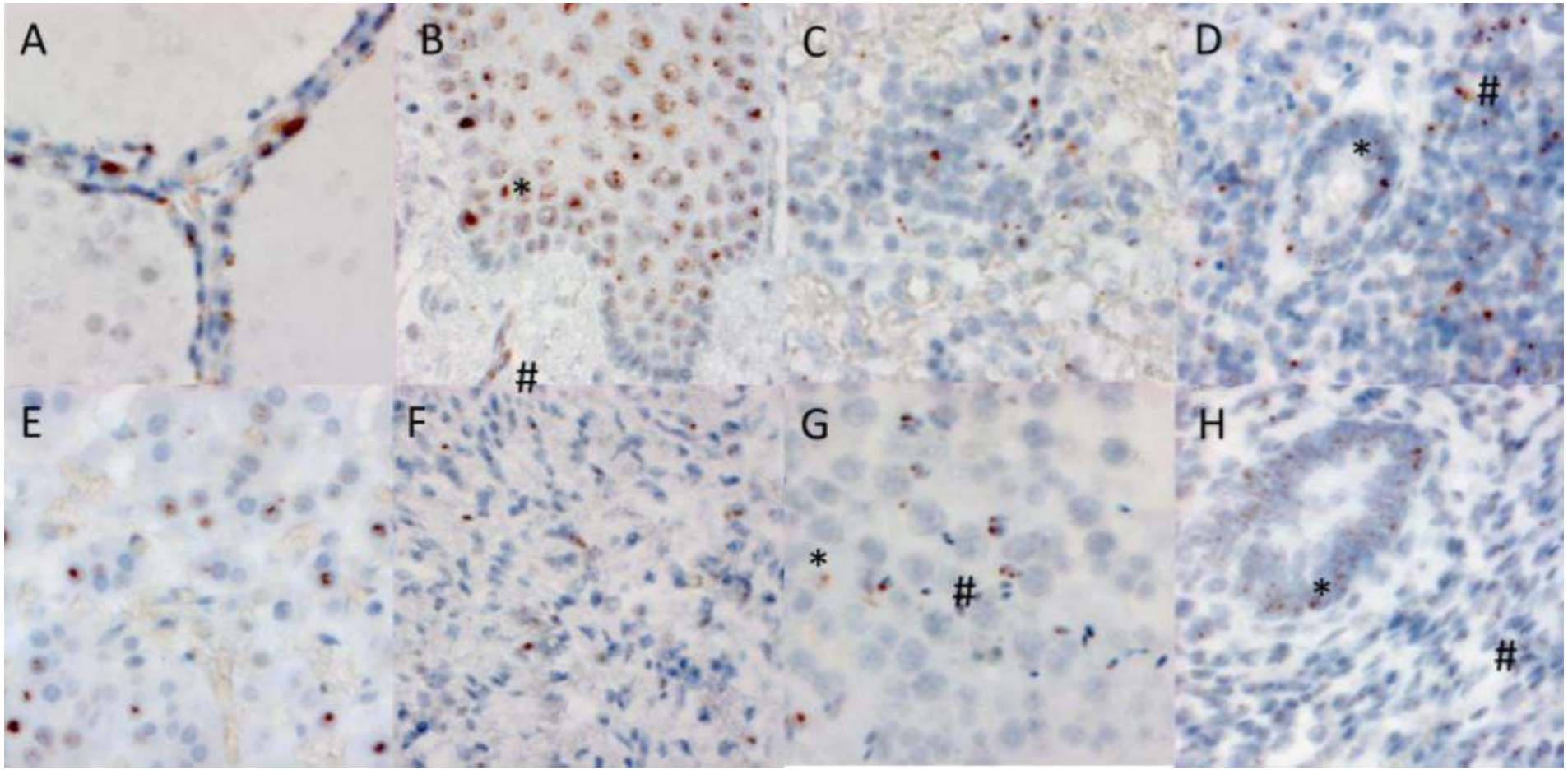
Evolution of antibody immunity to SARS-CoV-2

Christian Gaebler, Zijun Wang, Julio C. C. Lorenzi, Frauke Muecksch, Shlomo Finkin, Minami Tokuyama, Alice Cho, Mila Jankovic, Dennis Schaefer-Babajew, Thiago Y. Oliveira, Melissa Cipolla, Charlotte Viant, Christopher O. Barnes, Yaron Bram, Gaëlle Breton, Thomas Hägglöf, Pilar Mendoza, Arlene Hurley, Martina Turroja, Kristie Gordon, Katrina G. Millard, Victor Ramos, Fabian Schmidt, Yiska Weisblum, Divya Jha, Michael Tankelevich, Gustavo Martinez-Delgado, Jim Yee, Roshni Patel, Juan Dizon, Cecille Unson-O'Brien, Irina Shimeliovich, Davide F. Robbiani, Zhen Zhao, Anna Gazumyan, Robert E. Schwartz, Theodora Hatziioannou, Pamela J. Bjorkman, Saurabh Mehandru, Paul D. Bieniasz, Marina Caskey & Michel C. Nussenzweig -Show fewer authors

Memory B cells display clonal turnover after 6 months, and express a continually evolving antibody response

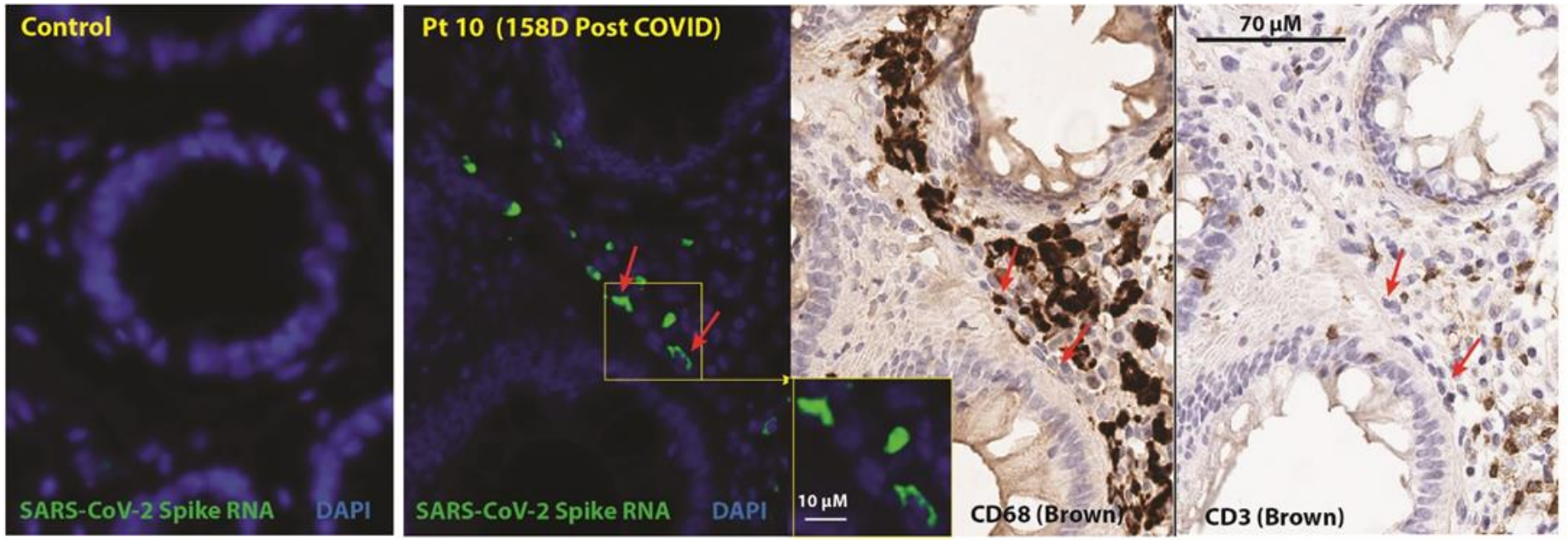
Viral protein detectable in intestinal biopsies obtained from asymptomatic individuals at month 4 in 7 out of 14 people

SARS-CoV-2 detected throughout the body (including brain) months after infection



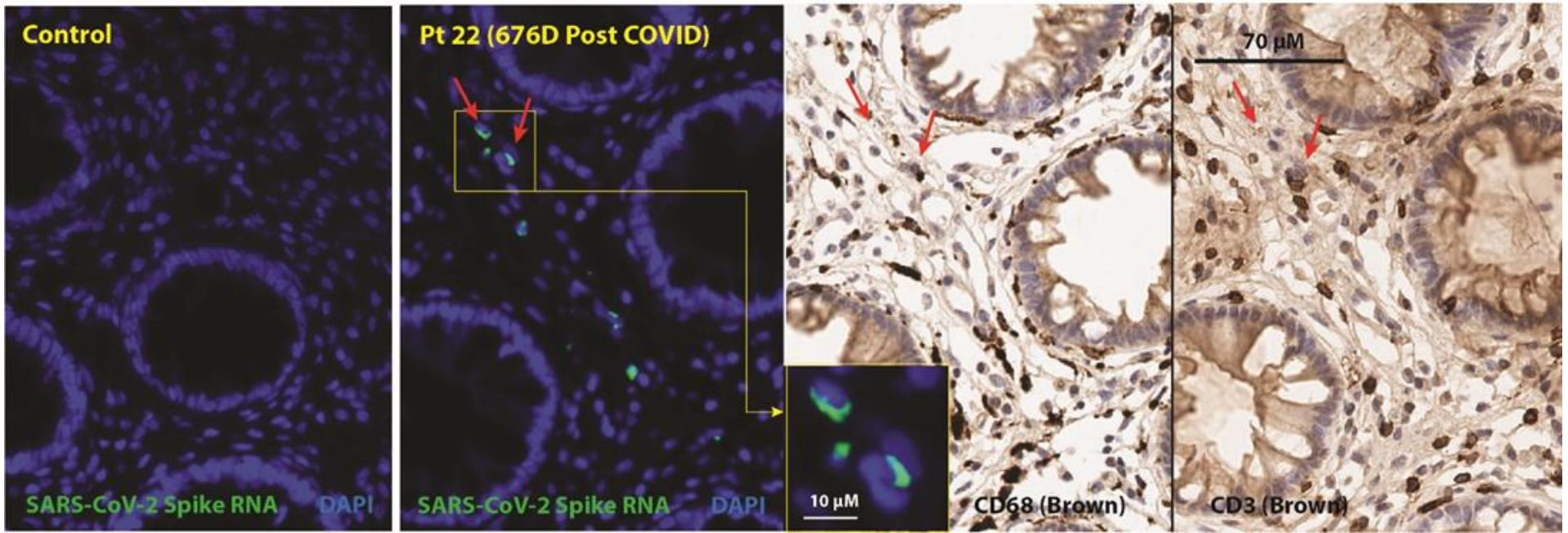
Stein et al. Nature. 2023

Persistent SARS-CoV-2 in Colorectal Tissue - LIINC



158 Days Post COVID-19

Spike RNA in Lamina Propria – some in macrophages



676 Days Post COVID-19

Spike RNA in Lamina Propria – some in macrophages

nature medicine

Unexplained post-acute infection syndromes

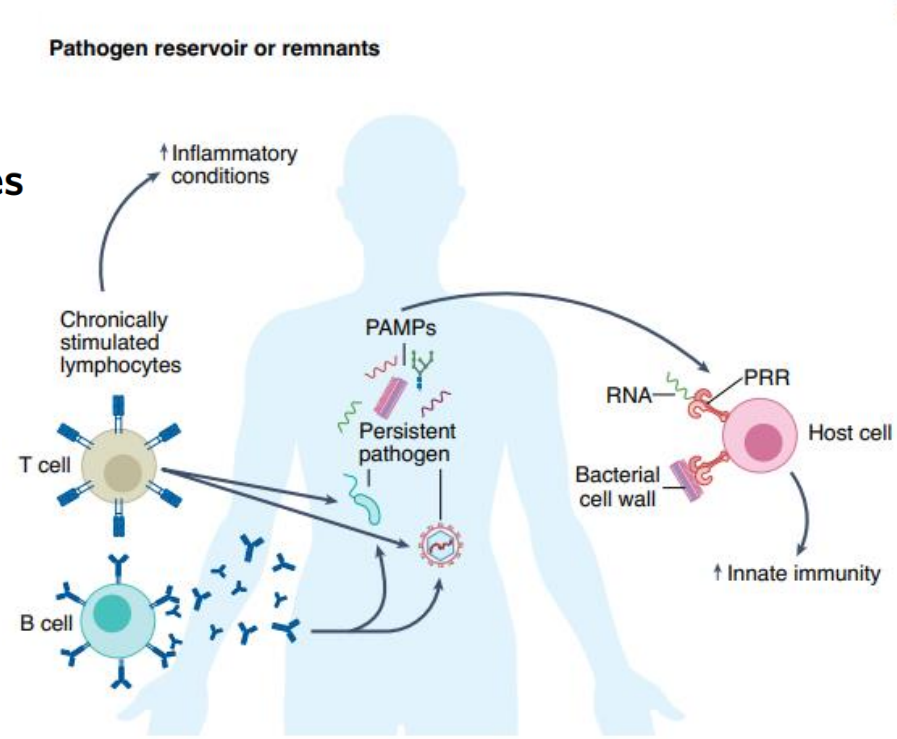
Jan Choutka[1]✉, Viraj Jansari[2], Mady Hornig[3] and Akiko Iwasaki[2,4,5,6]✉

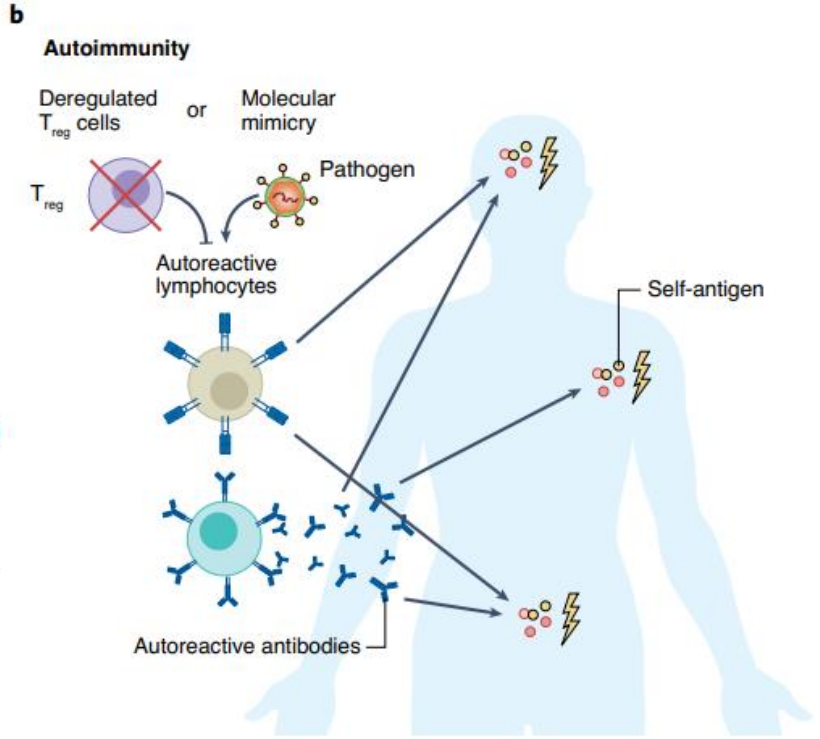
Table 1 | Overview of unexplained PAISs associated with documented infections

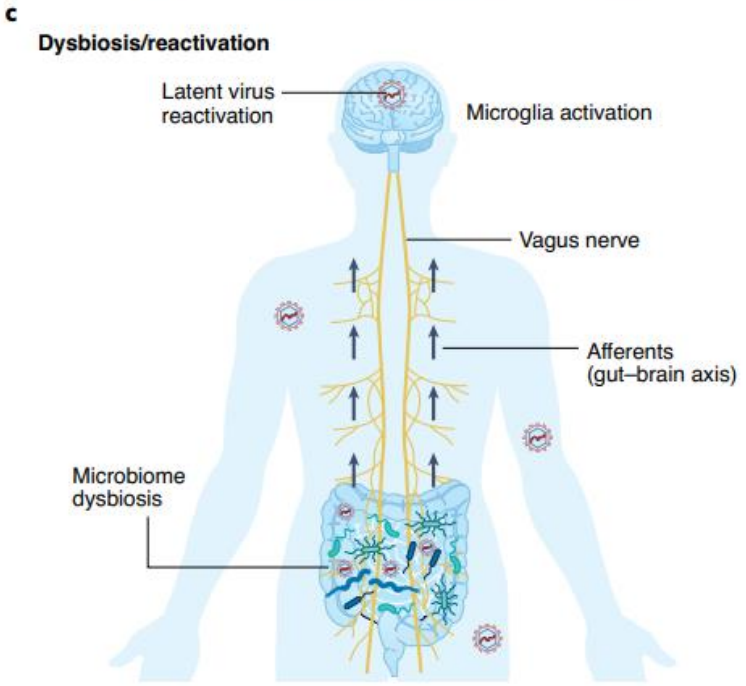
Pathogen	Name of PAIS
Viral pathogens	
SARS-CoV-2	Post-acute sequelae of SARS-CoV-2 infection (PASC) Post-acute COVID-19 syndrome (PACS) Long COVID
Ebola	Post-Ebola syndrome (PES) Post-Ebola virus disease syndrome (PEVDS)
Dengue	Post-dengue fatigue syndrome (PDFS)
Polio	Post-polio syndrome (PPS)
SARS	Post-SARS syndrome (PSS)
Chikungunya	Post-chikungunya chronic inflammatory rheumatism (pCHIK-CIR) Post-chikungunya disease
EBV	No name
West Nile virus	No name
Ross River virus[a]	No name
Coxsackie B[a]	No name
H1N1/09 influenza[a,b]	No name
VZV[a,b]	
Non-viral pat	
Coxiella burnetii	Q fever fatigue syndrome (QFS)
Borrelia[c]	Post-treatment Lyme disease syndrome (PTLDS)
Giardia lamblia[a,d]	No name

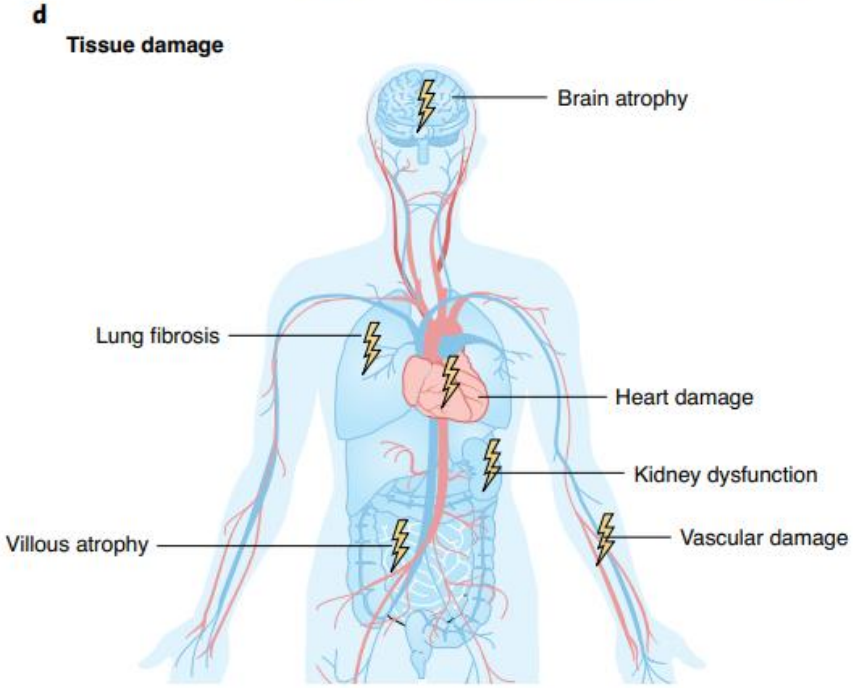
[a]Limited or very limited evidence base. [b]Association with increased use of ME/CFS diagnosis in health registry. [c]Contradicting or unclear evidence base. [d]Supporting evidence derives from a single outbreak in Norway.

Post-Campylobacter IBS









Concluding Thoughts

- **Clear overlap between post-infectious syndromes and chronic viral infections** (or at least persistence of microbial genetic material and proteins)
- **Just now appreciating the potential for "acute" infections to exhibit some degree of persistence leading to clinical morbidity**
- **Inflammation and dysregulated immunity persists for years following acute infection**
- **Reactivation of existing chronic viral infections in the setting of acute microbial illness may also play an etiologic role**
- **Tissue-based illnesses- need to do "deep dives" and not just study blood**

Concluding Thoughts

- **Etiology of Long COVID likely heterogenous but persistence of SARS-CoV-2 may lay behind many mechanisms**
  - clotting/microangiopathy
  - tissue damage / inflammation
  - dysregulated or autoreactive immune responses
- **The ”Post-COVID” era may have new immune/inflammatory set point that needs to be accounted for in prospective research/clinical diagnostics**
  - prior COVID-19 may influence outcomes in studies of other illnesses
  - need for contemporary control groups when studying inflammation/immunity

There may be <u>longer-term impact on human health</u>
(brain, cardiovascular, etc.)

LIINC is a massive team effort

LIINC Leadership Team
- Michael Peluso
- Tim Henrich
- Steve Deeks
- Bryan Greenhouse
- Isabel Rodriguez-Barraquer
- Jeff Martin
- Rachel Rutishauser
- Dan Kelly
- Priscilla Hsue
- Matt Durstenfeld

UCSF Division of HIV/ID/GM
Diane Havlir, Monica Gandhi, Matt Spinelli, Annie Luetkemeyer, Vivek Jain, Sulggi Lee, Laurence Huang

SCOPE/LIINC Clinical Research Team
Becky Hoh, Viva Tai, Meghann Williams, Monika Deswal, Mireya Arreguin, Dylan Ryder, Lynn Ngo, Sadie Munter, Melissa Buitrago, James Lombardo

LIINC-Coronavirus Neurocognitive Study Team
Joanna Hellmuth, Felicia Chow, Meredith Greene, Alexis Oddi

LIINC-Cardiovascular Impact Study Team
Priscilla Hsue, Matt Durstenfeld, Shreya Swaminathan, Victor Arechiga, Danny Li

LIINC-Social Science Team
John Sauceda, Edda Santiago Rodriguez

FIND/LIINC Clinical Epidemiology Team
Khamal Anglin, Scott Lu, Sarah Goldberg, Sujata Mathur, Jessica Chen, Gustavo Castellanos

Henrich Lab
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Monogram Biosciences
Chris Petropoulos, John Winslow, Ahmed Chenna, Brandon Yee

Greenhouse Lab

Andino Lab

Core Immunology Laboratory

AIDS Specimen Bank

Medical Students
Michelle Davidson, Hannah Sans, Jonathan Massachi, Kevin Donohue, Enrique Martinez, Allen Barnett, Alex Tang, Carrie Forman, Victoria Murray

Former LIINC Team Members
Marian Kerbleski, Heather Hartig, Fatima Ticas, Tamara Abualhsan, Andrea Alvarez, Yanel Hernandez, Emily Fehrman, Leo Torres, Jill Hakim, Keirstinne Turcios, Owen Jansen

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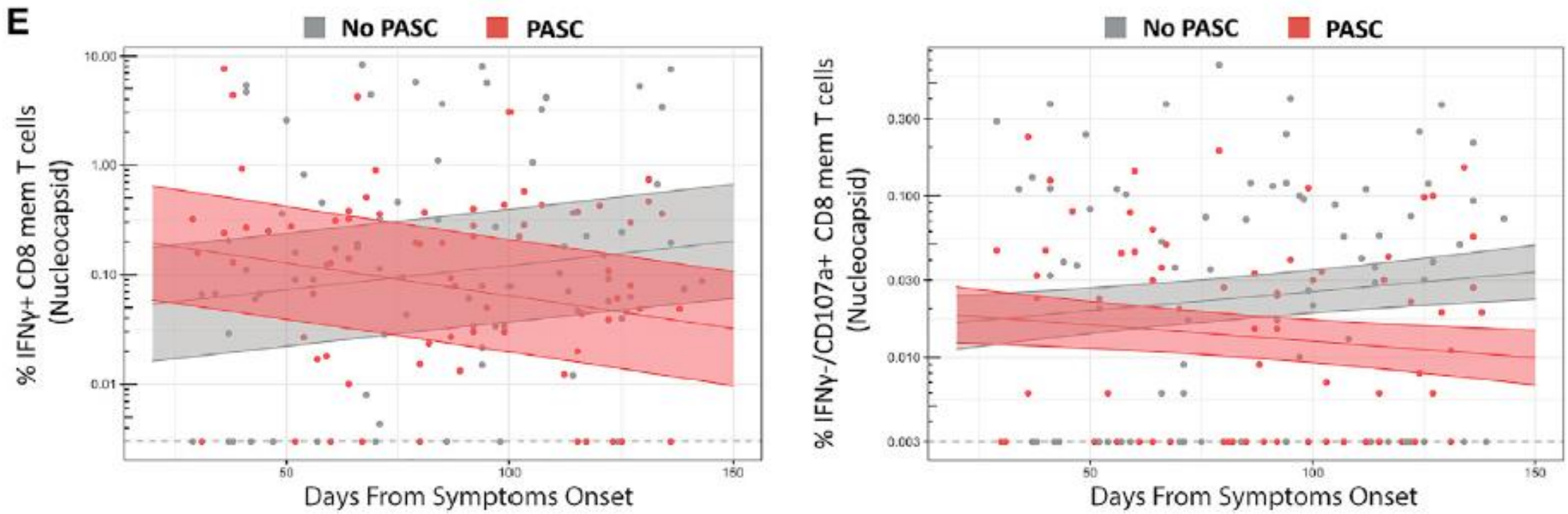
NIAID AI158013 (Gandhi/Spinelli)
K23AI157875 (Peluso)
UCSF Resource Allocation Program & CFAR

Greater Decline SARS-CoV-2-Specific CD8+ T Cell Responses in Participants who Develop PASC 4 Months after Acute Infection

Cell Reports

Article

Long-term SARS-CoV-2-specific immune and inflammatory responses in individuals recovering from COVID-19 with and without post-acute symptoms



Peluso et al. 2021

Persistent Inflammation 8 Months Following COVID-19