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HIV and Long COVID: Understanding the Compounding Risks

Biology * Public Health * Global Health

Introduction: Dual Viral Burden in the Post-Acute Era

As severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has transitioned into an endemic pathogen, research has increasingly focused on post-acute sequelae of SARS-CoV-2 (PASC), or Long COVID -- a heterogeneous syndrome affecting tens of millions globally with over two hundred symptoms persisting across multiple organ systems.[1] For people living with human immunodeficiency virus (HIV), the intersection of SARS-CoV-2 with a chronic retroviral infection creates magnified pathophysiological risks. Even under durable antiretroviral therapy (ART), HIV drives persistent immune activation, systemic inflammation, mucosal barrier damage, and cellular exhaustion. Current epidemiological data demonstrate that people living with HIV face a markedly elevated risk of developing Long COVID compared to HIV-negative populations, driven by compounding T-cell exhaustion, inflammasome hyperactivation, tissue viral reservoirs, and gut microbial translocation.[2]

The Epidemiological Landscape of Long COVID in HIV

Retrospective cohort studies and global meta-analyses establish a strong link between HIV status and Long COVID susceptibility. Analyzing statewide electronic health records (EHR) for 838,520 adults with COVID-19 (including 2,662 with HIV) between March 2020 and January 2022, researchers at the University of South Carolina Arnold School of Public Health found that 16.3 percent of people with HIV received a formal Long COVID diagnosis within 30 to 180 days, compared to 10.6 percent of HIV-negative individuals -- an adjusted 29 percent higher overall risk.[2] Vulnerability varied across organ systems, with neurological complications (headaches, neuropathic pain, cognitive fog, and sleep disruption) more than doubling.[2]

| Organ System / Diagnostic Category | | Adjusted Hazard Ratio | | Relative Risk Increase |

| Nervous System Diseases | | 2.04 | | 104% higher risk |

| Respiratory Diseases | | 1.78 | | 78% higher risk |

| Mental, Behavioral, and Neurodevelopmental | | 1.78 | | 78% higher risk |

| Endocrine and Metabolic Diseases | | 1.70 | | 70% higher risk |

| Genitourinary Disorders | | 1.59 | | 59% higher risk |

| Digestive System Diseases | | 1.47 | | 47% higher risk |

| Musculoskeletal Conditions | | 1.45 | | 45% higher risk |

A global meta-analysis pooling 17 studies across 39,405 people with HIV who contracted SARS-CoV-2 estimated that 52 percent developed at least one Long COVID symptom (odds ratio 2.20), led by persistent cough, fatigue, and asthenia.[4][5]

Acute COVID-19 hospitalization, unsuppressed HIV viral loads (>20 copies/mL) associated with blunted IgM/IgG antibody titers, and low CD4+ T-cell counts strongly predicted chronic sequelae.[4]

Yet clinical coding undercounts true prevalence. Evaluating over 4.6 million SARS-CoV-2 patients across PCORnet (1,369,896 patients; 11,964 with HIV) and N3C (3,312,355 patients; 23,931 with HIV) through April 2024, the RECOVER Initiative found elevated Long COVID odds using a symptom-based computed phenotype algorithm (adjusted OR 1.09 in PCORnet; 1.18 in N3C), but no association when relying strictly on ICD-10 Long COVID codes (OR ~1.0).[6] This gap reflects diagnostic overshadowing, wherein clinicians misattribute post-COVID fatigue or cognitive fog to baseline HIV, ART side effects, or aging.[6]

Immunological Drivers and Cellular Pathobiology

Even with ART-mediated viral suppression, people with HIV exhibit baseline systemic inflammation and altered lymphocyte homeostasis.[3] Elevated circulating cytokines -- signaling proteins primed by chronic retroviral persistence -- cause acute SARS-CoV-2 infection to trigger an exaggerated inflammatory cascade, with lower CD4+/CD8+ ratios correlating with expanded exhausted T-cell subsets.[3][7]

Under chronic antigenic stimulation from HIV and residual SARS-CoV-2, T cells undergo epigenetic and metabolic reprogramming into T-cell exhaustion.[8] Exhausted T cells lose proliferative capacity, fail to secrete interferon-gamma and TNF- , and upregulate inhibitory checkpoints (PD-1, TIM-3, CTLA-4).[8] People with HIV recovering from COVID-19 accumulate higher frequencies of exhausted PD-1+ SARS-CoV-2-specific CD4+ T cells alongside depleted functional memory CD8+ T cells.[3][9] Single-cell transcriptomics reveal CD8+ clusters upregulating TOX -- mirroring rapid exhaustion in cancer immunology -- that fail to clear viral remnants while sustaining tissue inflammation.[8][10] Concurrently, dual HIV and SARS-CoV-2 activation of the NLRP3 inflammasome in macrophages and central nervous system microglia releases IL-1 , IL-6, and TNF- alongside impaired oxygen exchange.[3][11][12] Elevated IP-10 and TNF- paired with depleted interferon-beta serve as key biomarkers of Long COVID in HIV.[3][4]

Viral Persistence, Reactivation, and the Gut-Systemic Axis

Unlike HIV, which integrates proviral DNA into the host genome, SARS-CoV-2 is a non-integrating RNA virus; however, biopsy and autopsy studies confirm SARS-CoV-2 RNA and Spike/Nucleoprotein antigens persist in gut, brain, lung, and cardiac tissues for over a year after nasopharyngeal clearance -- and up to 18 months in primate lungs.[1][14] Mucosal lymphoid depletion from prior HIV infection impairs tissue viral clearance, sustaining antigenic stimulation and triggering transient post-COVID HIV plasma "viral blips."[3][13] Exhausted CD8+ surveillance also permits reactivation of latent Epstein-Barr virus (EBV) and cytomegalovirus (CMV), driving neurocognitive fatigue.[1][3]

Simultaneously, dual infection disrupts the intestinal barrier and human microbiome. HIV-induced tight-junction degradation compounded by SARS-CoV-2 replication via intestinal ACE2 receptors allows commensal bacteria and endotoxins to translocate into the bloodstream.[16][18] Co-infected patients display elevated plasma

lipopolysaccharide (LPS), soluble CD14 (sCD14), and zonulin, alongside depletion of butyrate-producing Blautia and shifts in Akkermansia, perpetuating systemic inflammation.[3][16][17][18]

Microvascular, Endocrine, and Clinical Management Paradigms

Downstream, baseline retroviral endothelial stress predisposes patients to SARS-CoV-2 endotheliitis, platelet hyperactivation, and microclotting, causing capillary hypoxia, exercise intolerance, and B-cell dysfunction.[3][12] Viral tropism and microvascular ischemia in the adrenal cortex can also push subclinical adrenal insufficiency into overt hypocortisolism.[3] While candidate biomarkers (IP-10 and complement proteins C3, C4, and C5) await commercial standardization, clinicians must avoid dismissing normal routine imaging and integrate PASC rehabilitation into HIV primary care.[4][19][20][21]

| Model of Care | | Representative Setting | | Salient Clinical and Operational Features |

| Specialty-Based Model | | Academic PASC Centers | | Physiatrist-led multidisciplinary teams (neurology, cardiology, pulmonology); remote vital monitoring.[20][21] |

| Primary Care-Based Model | | Community HIV Clinics | | WHO-aligned integration of Long COVID, non-communicable diseases, and ART under one roof.[21][22] |

| Home-Based / Telehealth | | Virtual Rehabilitation | | Lowers geographic and socioeconomic barriers; delivers paced physical and occupational therapy.[21] |

World Health Organization (WHO) guidelines recommend integrating non-communicable and post-viral care directly into HIV clinics.[22] COVID-19 vaccination significantly lowers Long COVID incidence in people with HIV, though 2026 results from the NIH RECOVER-VITAL phase 2 randomized trial demonstrated that 15- and 25-day courses of nirmatrelvir-ritonavir (Paxlovid) did not significantly improve established Long COVID symptoms compared to placebo-ritonavir control, underscoring the need for targeted immunomodulatory and multi-pathway strategies.[15][19][23][24]

Conclusion: Translating Retroviral Lessons to Post-Acute Care

The convergence of HIV and SARS-CoV-2 produces a synergistic biological syndrome driven by PD-1+ T-cell exhaustion, NLRP3 inflammasome activation, tissue viral persistence, herpesvirus reactivation, and LPS-mediated microbial translocation. Overcoming diagnostic overshadowing through integrated HIV-PASC care models and applying antiretroviral reservoir pharmacology to post-viral therapeutics will be essential to reducing long-term morbidity in this vulnerable population.

Updates (Nov 15, 2026): Added 2026 NIH RECOVER-VITAL phase 2 trial results (Baden et al., The Lancet Infectious Diseases) showing extended 15- and 25-day nirmatrelvir-ritonavir courses did not significantly outperform placebo-ritonavir for established Long COVID, unnumbered section headings, and replaced ResearchGate, PMC reCAPTCHA, PubMed-only, and 502 NCI links with verified CrossRef DOIs.

Updates... (Nov 20, 2026): Corrected co-author attribution for Peluso & Antar (2023) per CrossRef metadata, added exact publication dates across all references,

deduplicated redundant reference entries, split combined inline citations, and aligned all 24 references 1:1 with inline tags.

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