Infectious Associated Chronic Illnesses

Translation from the Laboratory to the Clinic

Steven G. Deeks, MD

Professor of Medicine

Division of HIV, Infectious Diseases, and Global Medicine

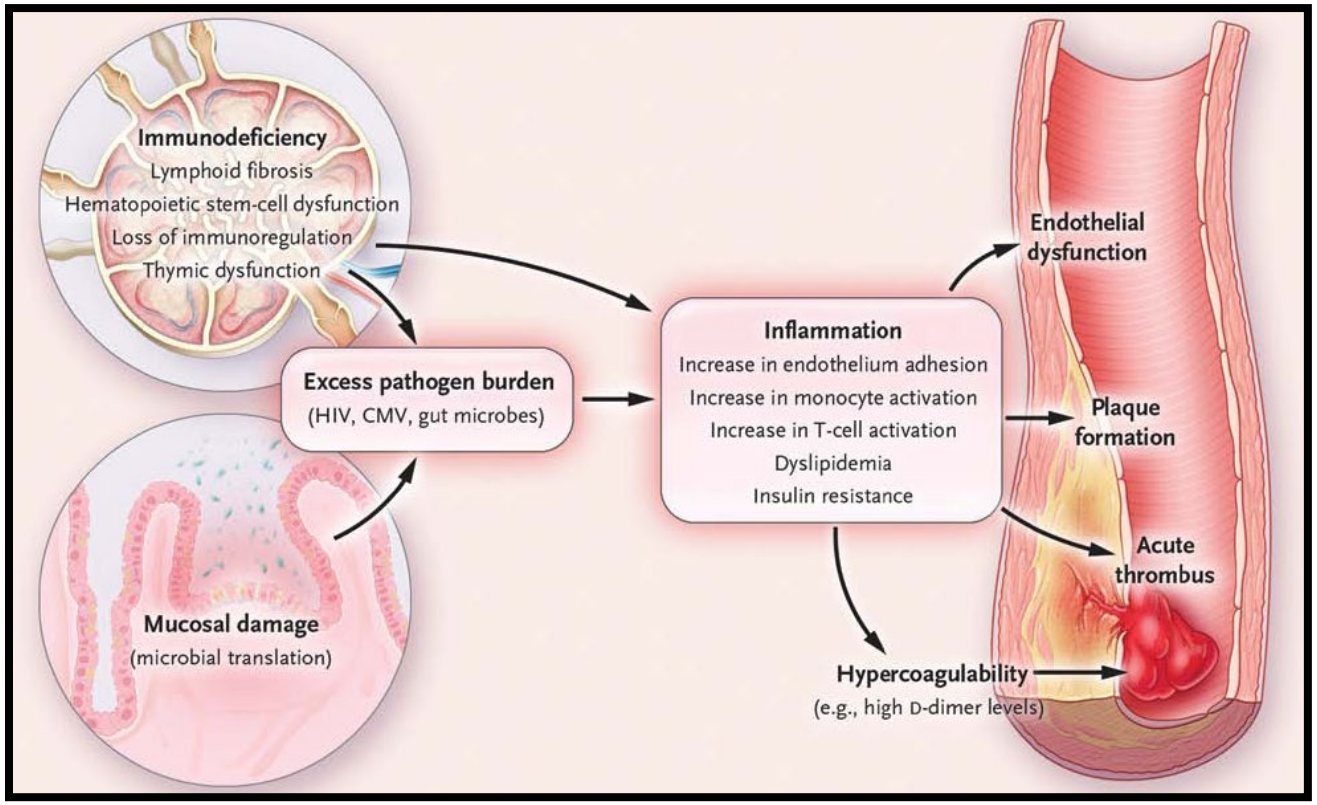
University of California, San Francisco

steven.deeks@ucsf.edu

Treated HIV is associated with excess risk of multiple morbidities, many also common after acute COVID, but "Long HIV" is not a thing

- Mortality (Kuller, PLoS Med, '08; Tien, JAIDS, '10; Tenorio, JID '14; Hunt, JID '14)
- Cardiovascular Disease (Duprez, Atherosclerosis, 2009)
- Cancer (Breen, Cancer Epi Bio Prev, 2010; Borges, AIDS, 2013)
- Venous Thromboembolism (Musselwhite, AIDS, 2011)
- COPD (Attia, Chest, 2014; Kirkegaard-Klitbo, AIDS, 2017)
- Renal Disease (Gupta, HIV Med, 2015; Kirkegaard-Klitbo, AIDS, 2017)
- Bacterial Pneumonia (Bjerk, PLoS One, 2014)
- Cognitive Dysfunction (Burdo, AIDS, 2013; Sattler, JAIDS 2015)
- Depression (Martinez, JAIDS, 2014)
- Frailty (Erlandson, JID, 2013; Piggott, CROI 2017, #133)
- Type 2 DM (Brown, Diabetes Care, 2010; Reid, AIDS, 2017)

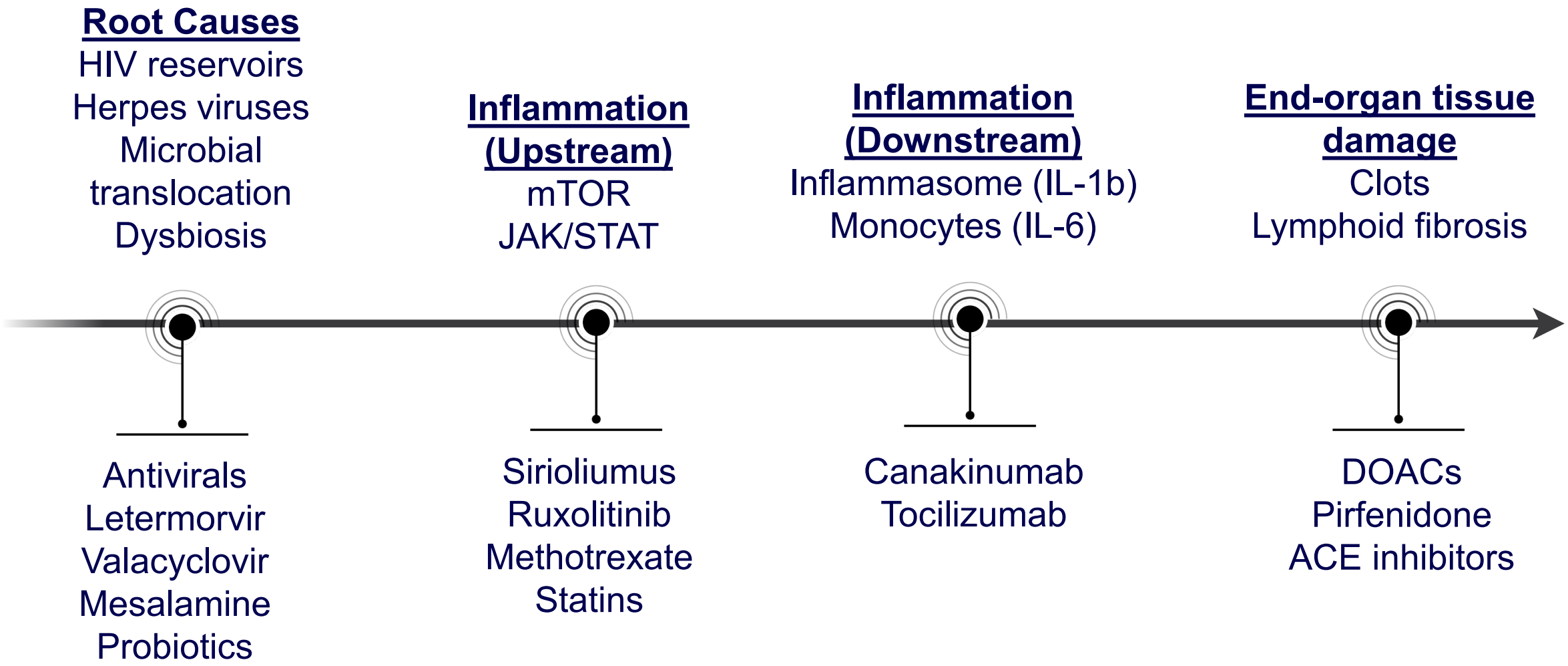
HIV-associated chronic illness: Mechanisms



- Acute and persistent HIV results in irreversible tissue damage, leading to chronic inflammation and hypercoagulability, which in turn causes vascular disease
- Inflammation enhanced by autoreactivity, microbial translocation (gut) and viral reactivation (EBV, CMV)

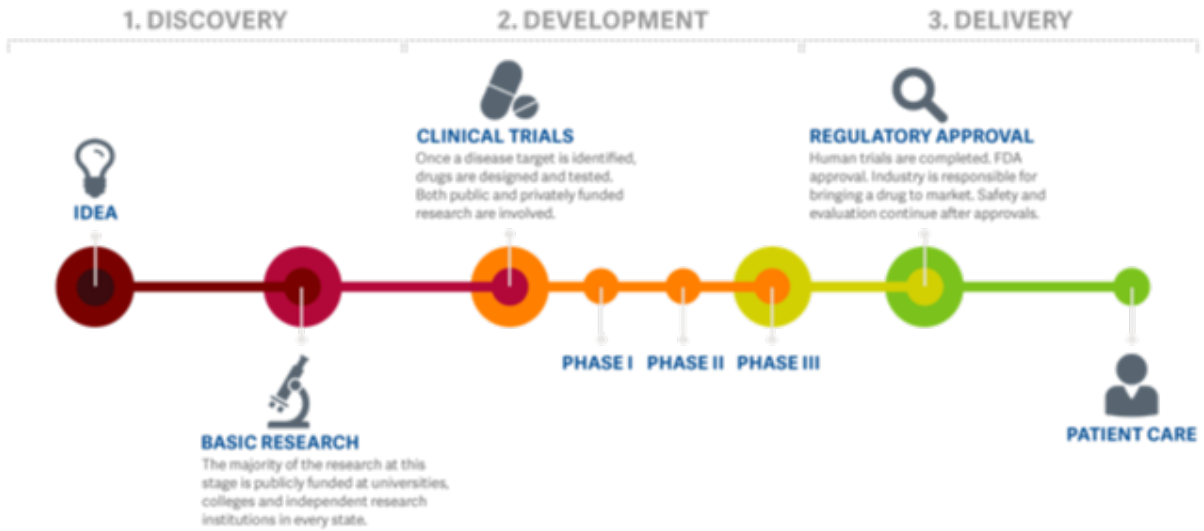
Deeks et al., NEJM 2012

Experimental medicine using available repurposed drugs resulted in characterization of how HIV causes chronic disease, which resulted in recent phase III studies of statins (REPRIEVE)

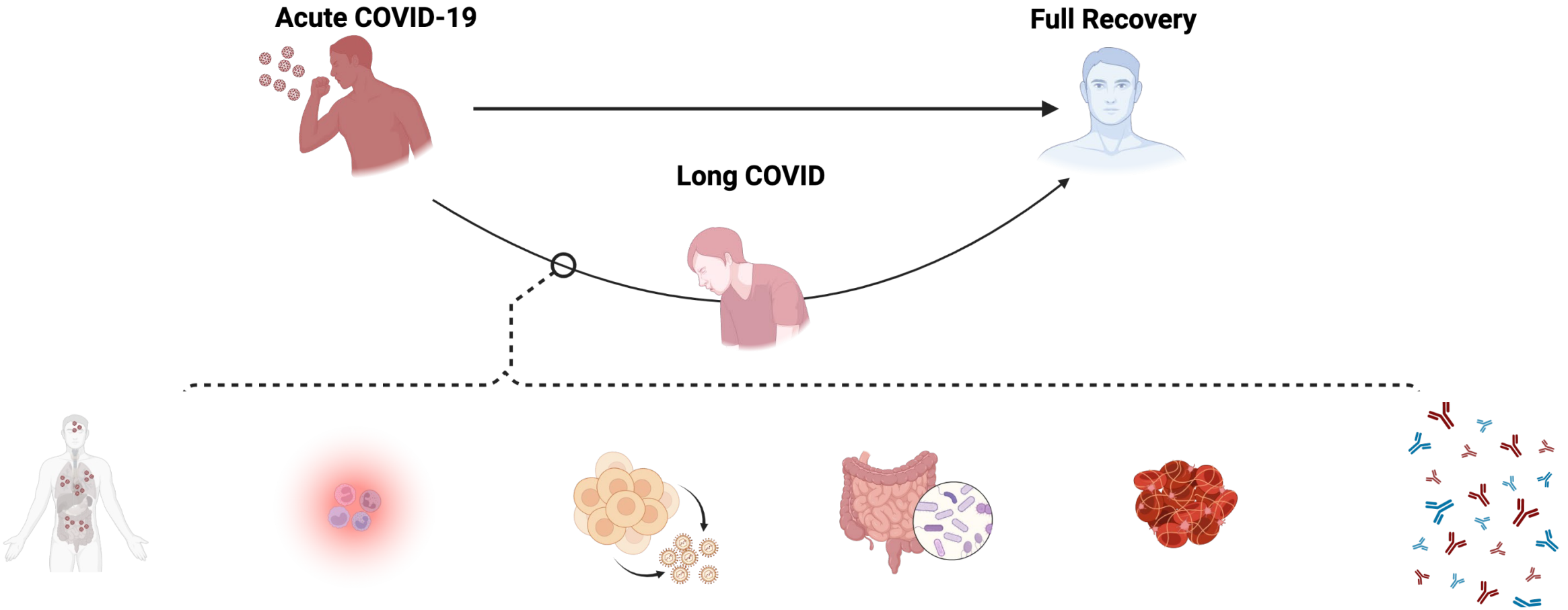


Experimental medicine

- Defining mechanisms of disease in people is difficult
  - Most studies are descriptive/observational
- Experimental medicine: Interrupt a pathway of interest in a controlled manner ("probe studies")
  - Often done by repurposing existing drugs
- When done correctly, these studies can provide proof-of-concept to encourage massive investment in developing new therapies



What causes infection-associated chronic illnesses?
Mechanistic pathways same as in treated HIV



Peluso & Deeks Trends in Immunology 2022

Long COVID and other IACIs: Mechanisms

Possible therapeutic strategies with repurposed drugs

Mechanism	Treatment
Acute viral infection with irreversible tissue damage	Antiviral drugs, therapeutic vaccines, anti-inflammatory drugs

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Persistent viral infection and ongoing tissue harm	Antiviral drugs, monoclonal antibodies, therapeutic vaccines, CAR-T cells

Long COVID and other IACIs: Mechanisms

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Mechanism	Treatment
Acute viral infection with irreversible tissue damage	Antiviral strategies
Persistent viral infection and ongoing tissue harm	Antiviral strategies
Inflammation • SARS-CoV-2 persistence • EBV reactivation • Mucosal breakdown • Dysbiosis • Loss of immunoregulation	Anti-inflammatory drugs: Steroids, JAK/STAT inhibitors, mAbs (anti-INF, anti-IL-6, anti-IL1β, anti-TNFα), IVIG EBV-directed therapies Probiotics Larazatide

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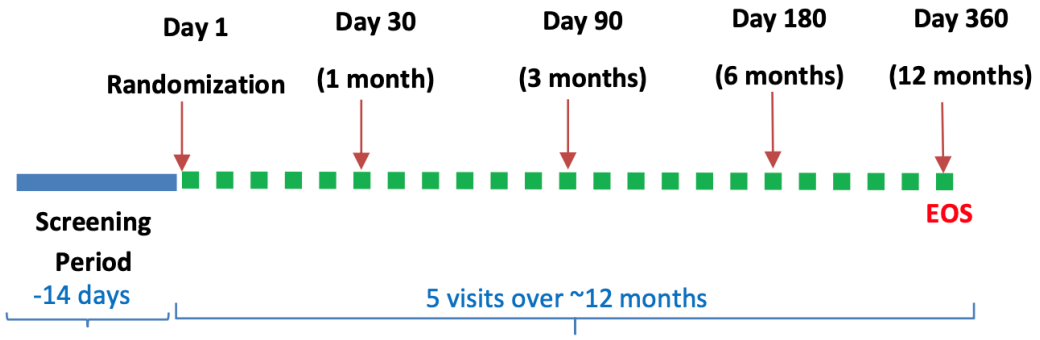
Acute viral infection with irreversible tissue damage	Antiviral strategies
Persistent viral infection and ongoing tissue harm	Antiviral strategies
Inflammation	Anti-inflammatory drugs
Auto-antibodies	IVIG, B cell-directed therapies
Microvascular disease (clotting, enthotheliitis)	Anti-platelet drugs (aspirin, clopidogrel), anticoagulants (DOACs), fibrinolytics

Immunotherapy for Neurological Post-Acute Sequelae of SARS-CoV-2 (IN-PASC) (NCT05350774)

- Background: IVIG has established efficacy in autoimmune syndromes (Guillain–Barré Syndrome)
  - Block Fc engagement on macrophages, reducing inflammation
- Study design: Randomized, placebo-controlled study of IVIG versus normal saline
  - IVIG: 0.4 grams/kg/day for five days
- Population: Neuro-Long COVID
- Endpoints: Multiple PROs, autonomic testing

Safety of an anti-SARS-CoV-2 safety of an anti-SARS-CoV-2 monoclonal antibody and response to treatment in individuals with Long COVID (OUTSMART-LC) (NCT05877508)



- Hypothesis: Viral particles persist in tissue/cellular reservoirs (replicating or not)
- AER002: RBD-specific monoclonal antibody with activity against all variants circulating through late 2022
- Design: 30 participants with LC dating back 2020-2022 randomized 2:1 to receive AER002 1200 mg or placebo (therapeutic levels > 6 months)
- Outcomes : PROMIS 29, COMPASS 31, Neurocognitive tests, 6 MWT, DSQ-PEM, inflammatory/coagulation markers, spike protein`

Evaluation of the Safety and Efficacy of Orally Administered NLRP3 Inhibitor, Dapansutrile on Individuals with Post-Acute Sequelae of COVID-19 (END-PASC)

- Background: Dapansutrile prevents NLRP3 inflammasome formation, in turn inhibiting IL-1β & IL-18
- Design: Randomized, placebo-controlled, 6 weeks followed by 6 weeks open label;
- Target Enrollment: 30 participants (2:1 randomization)
- Endpoints: Same as the AER002 study

Randomized trial EValuating baricitinib on pERSistent nEurologic and cardiopulmonary symptoms of Long COVID (REVERSE-LC, NCT05858515)

- Background: Inflammation predicts neuro-LC
  - Elevated cytokines (IL-6, IL-1b, TNFa) suggest microglial activation
  - JAK inhibitors disrupt these pathways and have proven efficacy/safety in acute COVID
- Design: Baricitinib versus placebo for 12 weeks in adults with neurocognitive impairment due to LC
- Outcomes: Neurocognitive function, CPET, PEM, QOL, cytokines, spike protein

RECOVER: Emerging clinical trials agenda

- RECOVER-VITAL: A Platform Protocol for Evaluation of Interventions for Viral Persistence, Viral Reactivation, and Immune Dysregulation in Post-Acute Sequelae of SARS-CoV-2 Infection (NCT05595369)
  - Paxlovid versus placebo
  - Paxlovid is also being studied at Stanford (NCT05576662) and Yale (NCT05668091)

- RECOVER-NEURO: A Platform Protocol for Evaluation of Interventions for Cognitive Dysfunction in Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)
  - Multiple interventions

RECOVER
Researching COVID to Enhance Recovery

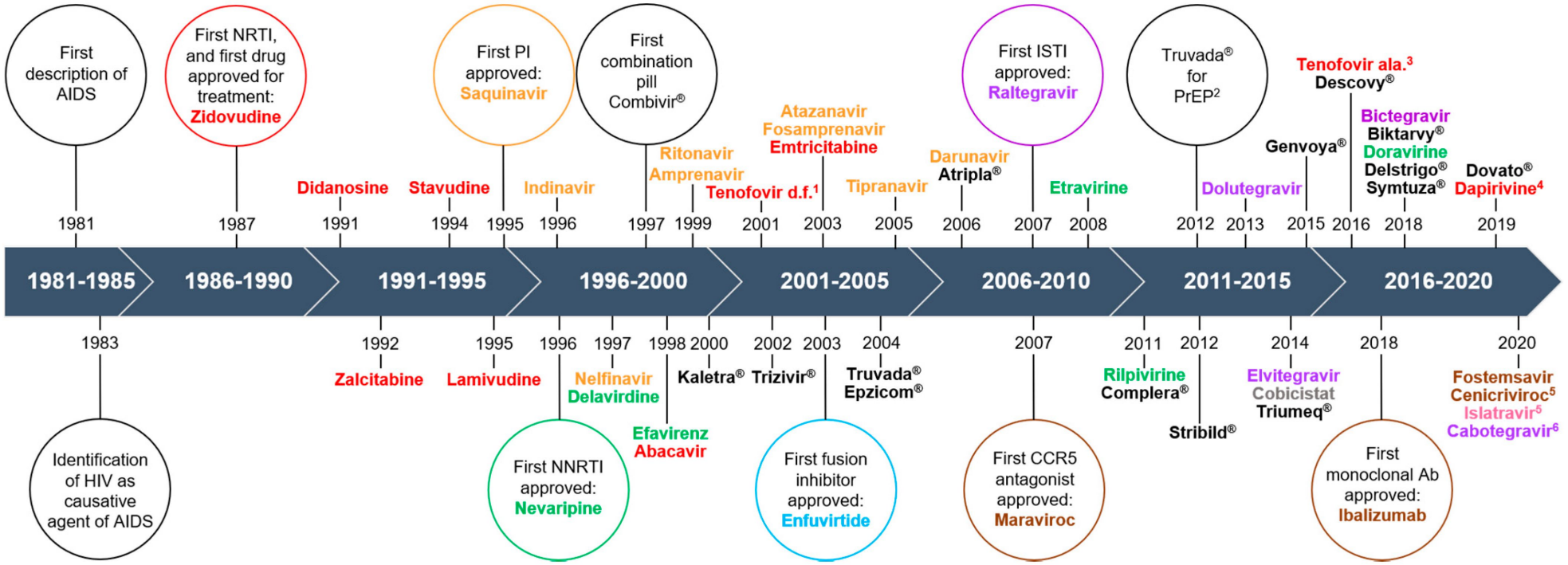
Popular treatments in the community

Social media, popular press, early POC studies

- Viral persistence: Therapeutic vaccines, antivirals (Paxlovid, mAbs)
- Endotheliitis (immune complexes): IVIG, steroids
- Dysautonomia: Pyridostigmine, vagus nerve stimulation, stellate ganglion block, IVIG, Enhanced External Counter Pulsation (EECP)
- Mast cell activation syndrome (MACS): Antihistamines
- Microvascular clots: Dialysis/apheresis (filtering), anticoagulation, fibrinolytics
- EBV reactivation: Valganciclovir, experimental antiviral therapies
- Leaky gut: Probiotics
- Neurocognitive symptoms: Naltrexone, HBOT
- Inflammation: Colchicine, IVIG, statins, steroids, monoclonal antibodies
- Autoantibodies: BC 007 (DNA aptermer; G-protein-coupled receptors)
- Mitochondria dysfunction: AXA1125, oxaloacetate
- Miscellaneous: Fasting

Validation of plasma HIV RNA was transformative

If pathogen persistence is the root cause, then this should happen for IACIs

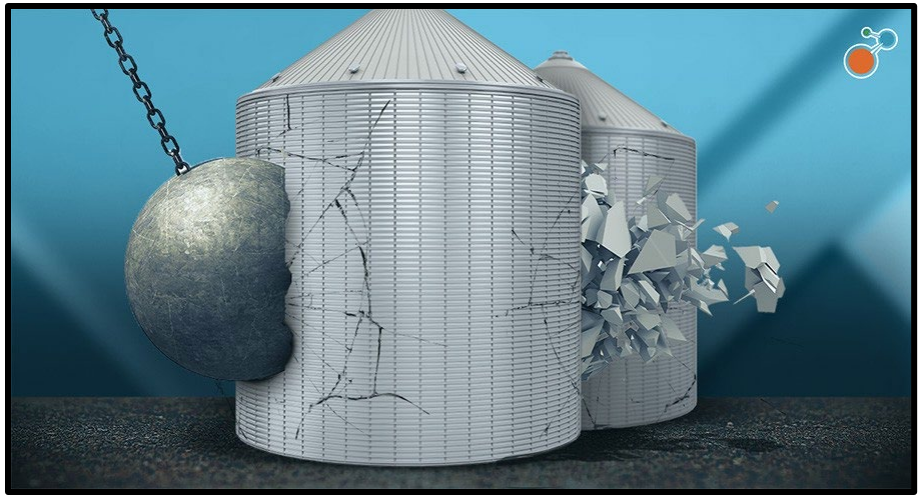


Cheny et al. Cells. 2021.

With a easily measured surrogate marker available, dozens of companies immediately entered the field, leading to > 25 drugs and rapid transformation of the disease

Multiple infections results in a chronic illness that is remarkably consistent, suggesting there must be a universal mechanism

- SARS (2003)
- EBV
- Zika
- Chikungunya
- Ebola/Marburg
- Enterovirus
- Borrelia burgdorferi (Lyme)
- Infection-associated ME and dysautonomia



Infection-associated chronic illnesses

- Stigma is disabling and needs to be addressed
- Mechanism: Multiple factors and pathways involved, suggesting need for combination approaches
  - Massive biorepository from 2020 exists and might provide most direct way to test mechanistic hypotheses
- Lack of clarity on mechanisms and endpoints are a major barrier for industry engagement
- Post-pandemic barriers: Limited interactions, we do not know each other (our strengths and weakness, our resources) and often do redundant work