

Passive Immunotherapy with Antibodies Against SARS CoV-2

- **Single donor convalescent plasma**
- **Hyperimmune Intravenous Immunoglobulin (IVIg)**
- **Monoclonal antibodies**

Single Donor Convalescent plasma

- **Regulated by the FDA through clinical trials, single patient eINDs and an expanded access program (EAP) facilitated by the Mayo Clinic**
- **As of June 6, 2020, clinicaltrials.gov listed 87 studies administering COVID-19 convalescent plasma**
 - **45 were open-label trials with no comparator**
 - **The remainder were randomized trials with a standard of care comparator (25); low-titer plasma comparator (8); crystalloid, IVIg or albumin comparator (8); or a comparator of packed red blood cells (1)**

Mayo Clinic Expanded Access Program

- As of June 5, 2020 from <https://www.uscovidplasma.org>:
 - 2,467 sites
 - 7,887 physicians
 - 27,110 patients
 - 20,093 infusions

Data From the Expanded Access Program

- **Cumulative data have been reported on the first 5000 patients**
 - **SAEs within 4 hours of transfusion were reported in 36 of 5000 (<1%) transfused patients**
 - **15 deaths (4 possibly or probably related to plasma treatment)**
 - **7 transfusion circulatory overload (TACO)**
 - **11 transfusion related acute lung injury (TRALI)**
 - **3 severe allergic reactions**
 - **Overall mortality was 14.9% at 7 days**

Joyner et al. Early Safety Indicators of COVID-19 Convalescent Plasma in 5,000 Patients.
<https://www.medrxiv.org/content/10.1101/2020.05.12.20099879v1>

Additional Published Data on Convalescent Plasma

- **Most open-label, case-control studies indicate some evidence of benefit**
- **A randomized, controlled trial of standard of care vs. standard of care + convalescent plasma in 109 individuals found:**
 - **Clinical improvement within 28 days in 51.9% of the convalescent plasma group vs 43.1% in the control group; $P = 0.26$**
 - **No significant difference in 28-day mortality 15.7% vs 24.0%; OR = 0.65, $P = 0.30$**

Data Supporting the Efficacy of Convalescent Plasma in Other Infectious Diseases

- **Open label, non-randomized trials**
 - **Ebola**
 - **Influenza**
 - **SARS**
- **Randomized, controlled trials**
 - **Argentine Hemorrhagic Fever (mortality of 16.5% vs. 1.1% in a cohort of 188 patients when treated within 8 days of symptoms)**

Hyperimmune IVIg

- **Licensed products for preventing post-transplant CMV disease (Ctyogam) and for post-exposure prophylaxis of varicella in high-risk individuals (VariZig)**
- **Two approaches are being taken to develop an anti-SARS-CoV-2 IVIg**
 - **Genetically modified cattle**
 - **Patients recovered from COVID-19**

IVIg From Genetically Engineered Cattle

- **SAB Biotherapeutics May 28 release:**
 - **Announced development of highly-potent neutralizing antibodies to SARS-CoV-2 that are four times higher than the most potent human convalescent plasma**
 - **Manufacturing of SAB-185 initiated on May 25**

IVIg From Convalescent Donors

- **Two randomized, placebo-controlled trials are being planned under the umbrella of ACTIV**
 - **Inpatient study in patients with ≤ 8 days of symptoms (+ remdesivir)**
 - **Outpatient study in patients at high risk of serious complications**
 - **Corporate partners include Emergent, Grifols and the Plasma Alliance (Takeda and CSL Behring providing products)**

Monoclonal Antibodies to SARS-CoV-2

- **At least 21 different products are in some stage of development**
- **Most target the spike protein**
- **Are undergoing pre-clinical evaluation as single agents and in combinations**
- **Clinical trials are being planned for both treatment and prophylaxis**

SARS-CoV-2 Spike Protein mAbs

REGENERON
science to medicine®

First in Human June 2020

Two SARS-CoV-2 spike directed mAbs from their humanized Ab mouse platform and isolated from human convalescent serum

First in human in hospitalized patients June 2020; NIAID/Regeneron trial in July, 2020

AbCellera

Lilly

First in Human MAY 2020

One or two SARS-CoV-2 specific mAbs, convalescent plasma

First in human hospitalized patients, May, 2020; NIAID/Lilly clinical trial late June, 2020.

VIR

First in Human JULY 2020

Vir mAb, S309, isolated from a SARS1 patient, cross-reacts with SARS-CoV-2

Collaboration under active discussion for nursing home trial

AstraZeneca

First in Human JULY 2020

AZ has selected a 2 mAb combination against the SARS-CoV-2 spike protein

Plan Phase I single dose escalation study in normal volunteers, August 2020 (DARPA)

Collaboration under active discussion (BARDA funding sought for Phase 3 trial)

The Rockefeller University
SCIENCE FOR THE BENEFIT OF HUMANITY
1901

First in Human Fall 2020

Michel Nussenzweig developed cocktail of two mAbs isolated from convalescent plasma, target two non-overlapping epitopes of the receptor binding domain

Bristol Myers Squibb will manufacture antibodies

ACTIV Clinical Trials with Monoclonal Antibodies in Planning

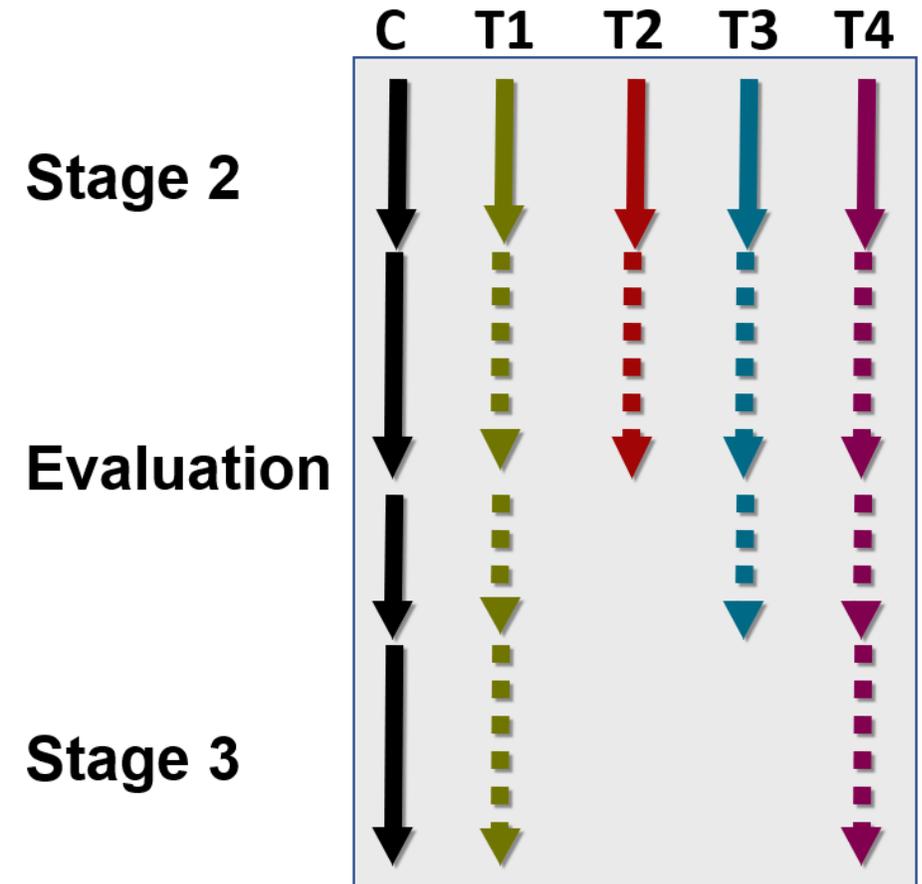
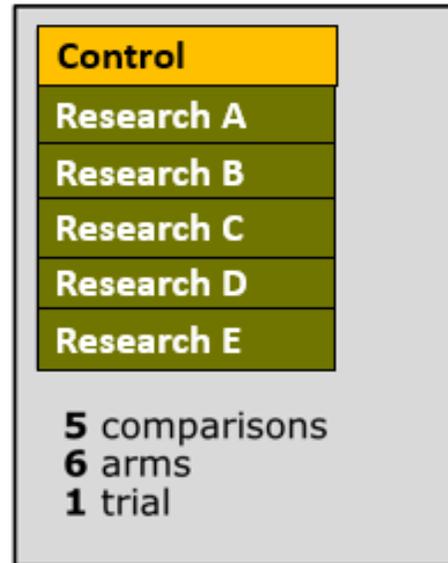
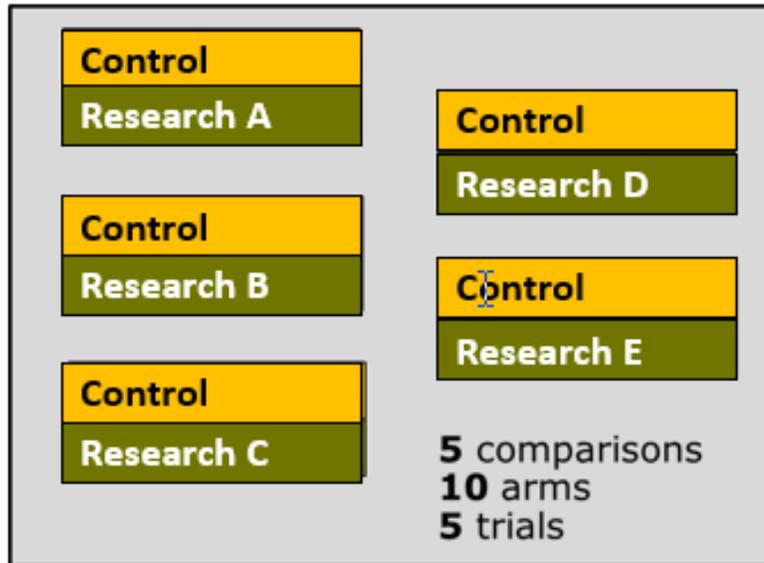
- **ACTIV-2 is an outpatient study to be done by the NIAID AIDS Clinical Trials Network (ACTG)**
- **ACTIV-3 is an inpatient study to be done by the NIAID International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) + the NHLBI Prevention and Early Treatment of Acute Lung Injury (PETAL) + the Veterans Administration Network**
- **Both trials combine classic Phase 2 and Phase 3 elements into a single study using an ordinal scale for outcomes**

An Evolving Ordinal Scale is Used to Classify Disease Progression in COVID-19

	Category	
Better	1	No limiting symptoms due to COVID-19
	2	Limiting symptoms due to COVID-19
	3	Moderate end-organ dysfunction
Worse	4	Serious end-organ dysfunction
	5	Life-threatening end-organ dysfunction
	6	End-organ failure
	7	Death

Includes key non- respiratory elements of progression including thrombosis and dialysis

ACTIV-3; A Multi-Arm, Multi-Stage Trial



Summary

- **A robust program examining the role of passive transfer of anti-SARS-CoV-2 antibodies is in place**
- **There is great enthusiasm for the use of convalescent plasma; the approach appears relatively safe; efficacy data are anxiously awaited**
- **Clinical trials of additional antibody products are slated to begin this summer; they include**
 - **Hyperimmune IVIg**
 - **Monoclonal Antibodies**