The Adaptive COVID-19 Treatment Trial (ACTT; DMID/NIAID; John Beigel, PI)

- A randomized, controlled trial with an adaptive platform
- Eligibility: Adult patients hospitalized with COVID-19 and evidence of pulmonary disease
- Primary Endpoint: Time to recovery (ordinal scale 1, 2 or 3)
- Timeline: Study opened Feb. 21, 2020
- Has completed first three versions; enrolling into the fourth
  - ACTT-1: Standard of care vs. remdesivir
  - ACTT-2: Remdesivir vs. remdesivir + baricitinib
  - ACTT-3: Remdesivir vs. remdesivir + interferon-β
  - ACTT-4: Dex + remdesivir vs. baricitinib + remdesivir
NIAID Adaptive Randomized, Controlled Treatment Trial for COVID-19

United Kingdom
- Royal Victoria Infirmary
- Guy's & St. Thomas' NHS Foundation Trust
- Royal Sussex County Hospital
- St. James's University Hospital
- Churchill Hospital
- University Hospital - Bonn
- University Hospital - Bonn
- University Hospital - Cologne

Germany
- University of Minnesota Medical Center
- University of Rochester Medical Center
- University of Wisconsin-Madison
- Penn State Health Milton S. Hershey Medical Center
- Northwestern University
- University of Rochester Medical Center
- University of Chicago
- University of Pennsylvania
- University of North Carolina at Chapel Hill
- University of Pittsburgh
- University of Virginia

Denmark
- Aalborg University Hospital
- Aarhus University Hospital
- Odense University Hospital

South Korea
- Seoul National University Hospital – Bundang

Japan
- National Center for Global Health and Medicine
- INER Nutrición

Mexico
- National Center for Global Health and Medicine

Singapore
- Hospital Clinic Barcelona
- National Centre for Infectious Diseases (NCID)

1,062 enrollees at trial close, 4/19/2020
Time to Recovery* for Remdesivir and Placebo Arms

Proportion Recovered

Remdesivir

Placebo

<table>
<thead>
<tr>
<th>Ordinal Scale</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>Not hospitalized, full activity</td>
</tr>
<tr>
<td>2*</td>
<td>Not hospitalized, limited activity</td>
</tr>
<tr>
<td>3*</td>
<td>Hospitalized, Non-medical</td>
</tr>
<tr>
<td>4</td>
<td>Hospitalized, not requiring O₂</td>
</tr>
<tr>
<td>5</td>
<td>Hospitalized, requiring O₂</td>
</tr>
<tr>
<td>6</td>
<td>High-flow O₂ or non-invasive vent.</td>
</tr>
<tr>
<td>7</td>
<td>Mechanical vent. or ECMO</td>
</tr>
<tr>
<td>8</td>
<td>Death</td>
</tr>
</tbody>
</table>

P<0.001

DOI: 10.1056/NEJMoa2007764
WHO Solidarity Trial

- 405 sites in 30 countries
- Death through 28 days
- Randomization to remdesivir ongoing

### Intervention Results

<table>
<thead>
<tr>
<th>Intervention</th>
<th>N</th>
<th>Mortality Rate</th>
<th>Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remdesivir</td>
<td>2750</td>
<td>12.5 / 12.7</td>
<td>0.95</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>954</td>
<td>10.2 / 8.9</td>
<td>1.19</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir</td>
<td>1411</td>
<td>9.7 / 10.3</td>
<td>1.00</td>
</tr>
<tr>
<td>Interferon-beta +/- Lopinavir/Ritonavir</td>
<td>2063</td>
<td>12.9 / 11.0</td>
<td>1.16</td>
</tr>
</tbody>
</table>

Stratified rate ratio, 0.95 (95% CI 0.81-1.11), p=0.50 by log-rank test

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SARS-CoV-2 and the Surface Spike Protein

Envelope protein (E)
Matrix protein (M)
Nucleoprotein (N) and viral RNA
N-Terminal Domain (NTD)
Receptor Binding Domain (RBD)

Images: RML, Florian Krammer and NIAID VRC
Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Trials (1)

- ACTIV-2: 2-stage adaptive trial in outpatients
  - Initially studied placebo vs. MoAb bamlanivimab (ACE2)
  - Currently open-label bam; will soon study a second Ab
- ACTIV-3: 2-stage adaptive trial in hospitalized patients
  - Initially studied remdesivir + (placebo vs. bamlanivimab)
    - No evidence of efficacy at Stage 1 (in press, NEJM)
  - Version 2.0 will look at antibodies from two companies
    - 1 cross-reacts with SARS-CoV-1; a highly conserved site
    - The other is a combination of two antibodies
Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Trials

- **ACTIV-5/Big Effect Trial (DMID/NIAID):** Several different interventions looking for a big effect to then take into one of the other ACTT or ACTIV platforms
  - Currently looking at two agents + remdesivir:
    - Risankizumab (anti-IL23A, licensed for treating psoriasis)
    - Lenzilumab (anti-GM-CSF, under investigation for cytokine-release syndrome)
Two Randomized, Controlled Trials of Immune IVIg

Inpatients

OUTPATIENTS

INSIGHT 013 (n=500)

INSIGHT 012 (n=1000)
There are Currently 2543 Studies for the Treatment of COVID-19 Listed on ClinicalTrials.gov
Coronavirus Disease 2019 (COVID-19) Treatment Guidelines

http://covid19treatmentguidelines.nih.gov
**NIH Treatment Guidelines Panel Recommendations for Treatment of COVID-19**

**Disease Severity**

<table>
<thead>
<tr>
<th>Not Hospitalized, Mild to Moderate COVID-19</th>
<th><strong>Panel’s Recommendations</strong></th>
</tr>
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<tbody>
<tr>
<td></td>
<td>There are insufficient data to recommend either for or against any specific antiviral or antibody therapy. SARS-CoV-2 neutralizing antibodies (bamlovlavimab or casirivimab plus imdevimab) are available through EUAs for outpatients who are at high risk of disease progression. These EUAs do not authorize use in hospitalized patients.</td>
</tr>
<tr>
<td></td>
<td><strong>Dexamethasone</strong> should not be used (AII).</td>
</tr>
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<tr>
<th>Hospitalized* But Does Not Require Supplemental Oxygen</th>
<th><strong>Panel’s Recommendations</strong></th>
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<tr>
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<td>There are insufficient data to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, the use of remdesivir may be appropriate.</td>
</tr>
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<td></td>
<td><strong>Dexamethasone</strong> should not be used (AIIa).</td>
</tr>
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<tr>
<th>Hospitalized* and Requires Supplemental Oxygen (But Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)</th>
<th><strong>Panel’s Recommendations</strong></th>
</tr>
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<tbody>
<tr>
<td>Use one of the following options:</td>
<td>(But Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)</td>
</tr>
<tr>
<td>• Remdesivir(b,c) (e.g., for patients who require minimal supplemental oxygen) (BIIa)</td>
<td>(But Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)</td>
</tr>
<tr>
<td>• Dexamethasone* plus remdesivir(b,c) (e.g., for patients who require increasing amounts of supplemental oxygen) (BIII)c</td>
<td>(But Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)</td>
</tr>
<tr>
<td>• Dexamethasone* (e.g., when combination therapy with remdesivir cannot be used or is not available) (BII)</td>
<td>(But Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)</td>
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<th>Hospitalized* and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation</th>
<th><strong>Panel’s Recommendations</strong></th>
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<td>Use one of the following options:</td>
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<td>• Dexamethasone**(a)** (AII)</td>
<td>(But Does Not Require Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation)</td>
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<tr>
<td>• Dexamethasone* plus remdesivir**(a)** (BIII)c</td>
<td>(But Does Not Require Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation)</td>
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<th>Hospitalized* and Requires Invasive Mechanical Ventilation or ECMO</th>
<th><strong>Panel’s Recommendations</strong></th>
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<td><strong>Dexamethasone</strong>(a) (AII)</td>
<td>(But Does Not Require Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation)</td>
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**Rating of Recommendations:**
- **A** = Strong
- **B** = Moderate
- **C** = Optional

**Rating of Evidence:**
- **I** = One or more randomized trials without major limitations
- **IIa** = Other randomized trials or subgroup analyses of randomized trials
- **IIb** = Nonrandomized trials or observational cohort studies
- **III** = Expert opinion

- **March 20** – request from HHS
- **March 22** – initial 37 members identified; 6 USG agencies; 8 professional societies
- **March 24** – first meeting
- **April 7** – first release ready
- **April 21** – final approval
- Since then:
  - 6 major revisions
  - 8 rapid communications
  - 7,213,718 page views