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

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

<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>

DOI: 10.1056/NEJMoa2007764
WHO Solidarity Trial

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

<table>
<thead>
<tr>
<th>Intervention</th>
<th>N</th>
<th>Mortality Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remdesivir</td>
<td>2750</td>
<td>0.95</td>
</tr>
<tr>
<td>Hydroxychlorquine</td>
<td>954</td>
<td>1.19</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir</td>
<td>1411</td>
<td>1.00</td>
</tr>
<tr>
<td>Interferon-beta +/− Lopinavir/Ritonav</td>
<td>2063</td>
<td>1.16</td>
</tr>
</tbody>
</table>

SARS-CoV-2 and the Surface Spike Protein

Images: RML, Florian Krammer and NIAID VRC
• 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)
Immune IVIg Studies
Two Randomized, Controlled Trials of Immune IVIg

- Takeda
- Grifols
- CSL/Behring
- Emergent

INSIGHT 013 (n=500) Inpatients
INSIGHT 012 (n=1000) Outpatients
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
DISEASE SEVERITY | PANEL'S RECOMMENDATIONS
--- | ---
No Hospitalized, Mild to Moderate COVID-19 | There are insufficient data to recommend either for or against any specific antiviral or antibody therapy. SARS-CoV-2 neutralizing antibodies (bamlanivimab 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 hospital patients. Dexamethasone should not be used (Alll).

Hospitalized but Does Not Require Supplemental Oxygen | Dexamethasone should not be used (Alla). 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.

Hospitalized and Requires Supplemental Oxygen (but Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO) | Use one of the following options:
- Remdesivir\(^{b,c}\) (e.g., for patients who require minimal supplemental oxygen) (BIIa)
- Dexamethasone\(^{d}\) plus remdesivir\(^{h+i}\) (e.g., for patients who require increased amounts of supplemental oxygen) (BIII)\(^{h+i}\)
- Dexamethasone\(^{d}\) (e.g., when combination therapy with remdesivir cannot be used or is not available) (BII)

Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation | Use one of the following options:
- Dexamethasone\(^{d}\) (AI)
- Dexamethasone\(^{d}\) plus remdesivir\(^{h+i}\) (BIII)\(^{h+i}\)

Hospitalized and Requires Invasive Mechanical Ventilation or ECMO | Dexamethasone\(^{d}\) (AI)

**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