Treatment of Viral Infections including COVID-19

Dr. Sujith J Chandy MBBS., MD., PhD., FRCP(Edin)
Director, ReAct Asia Pacific
Professor, Clinical Pharmacology
Christian Medical College, Vellore, India
What is a Virus?

An infective agent (intracellular parasite) ...... 
..... consists of a nucleic acid molecule in a protein coat / capsid 
.....able to multiply only within the living cells of a host
Types of Virus

**DNA VIRUS**
- Pox virus
- Herpes virus
- Adeno virus
- Hepadna virus
- Papilloma virus

**RNA VIRUS**
- Rhabdo virus
- Rubella virus
- Picorna virus
- Orthomyxo virus
- Paramyxo virus
- Retro virus
- Corona virus

Most DNA viruses assemble in the nucleus; most RNA viruses in cytoplasm
The more ‘in’famous viruses in the last decade
Stages of viral replication & Targets for treatment

- Cell Entry
- Uncoating
- Translation of viral proteins
- Posttranslational modification
- Release
Mechanisms of anti-viral action

• Inhibition of viral enzymes - viral DNA and RNA polymerase

• Viral protein glycosylation, virus assembly, new virus particle transport, and virus release.

• Other mechanisms - inhibition of ACE2 cellular receptor.

• Acidification at the surface of the cell membrane inhibiting fusion of the virus, and immunomodulation of cytokine release
Problems with antiviral therapy

• Drugs interfere with host cell metabolism:
  – this can lead to adverse effects

• Adequate concentrations of drug need to be accumulated inside cell:
  - for good effect

• Peak viral replication associated with symptoms:
  – therapy must be started earlier to be effective
Classification of antiviral drugs according to their therapeutic uses

- **Anti-herpes virus agents**
  Acyclovir, Famcyclovir, Gancyclovir, Idoxuridine, Foscarnet, Fomivirsen, Pencyclovir, Trifluridine, Tromantadine, Valacyclovir, Valgancyclovir, Vidarabine, Cidofovir, Docosanol

- **Anti-influenza Agents**
  Amantadine, Oseltamivir, Peramivir, Rimantadine, Zanamivir

- **Other antiviral agents**
  Fomivirsen, Enfuvirtide, Imiquimod, Interferon, Ribavirin, Viramidine

- **Antiretroviral Agents**
  - **NRTIs**: Zidovudine, Didanosine, Stavudine, Zalcitabine, Lamivudine, Abacavir, Tenofovir
  - **NNRTIs**: Nevirapine, Efavirenz, Delavirdine
  - **Protease Inhibitors**: Saquinavir, Indinavir, Atazanavir, Ritonavir, Nelfinavir, Amprenavir, Lopinavir, Tipranavir
Acyclovir

• Guanosine derivative
• Mechanism:
  1. Inhibits herpes virus DNA polymerase
  2. Incorporated into viral DNA – stops DNA strand elongation

• PK – widely distributed, enters CSF & cornea
• Preparations – tablet, vial, cream, eye ointment
• ADR – burning sensation (topical), rashes (IV)
Acyclovir - Uses

• Genital Herpes Simplex
• Mucocutaneous HSV
• HSV encephalitis – IV therapy
• HSV keratitis – eye ointment
• Herpes Zoster – IV or oral. Ointment can be applied on ulcer
• Chicken pox – Given IV for immunocompromised individuals
Other Herpes Group agents

• Ganciclovir – Used mainly in cytomegalovirus (CMV) infections. Can cause bone marrow depression, psychiatric disturbances

• Idoxuridine – Mainly used in eye for varicella zoster, HSV keratoconjunctivitis

• Vidarabine – Less side effects than Idoxuridine. Alternative to Acyclovir also
Other antiviral agents

Amantadine:
- Inhibits viral particle assembly
- Used for prophylaxis of influenza A epidemics

Ribavarin:
- Inhibits viral RNA synthesis
- Broad spectrum – influenza A & B, RSV, Lassa fever etc.
- Available orally & aerosol

Gammaglobulins:
- Pooled gammaglobulins contain antibodies against various viruses
- Antibodies directed against virus envelope. Prevents attachment of virus to host cell
- Used for hepatitis, rabies, polio
Interferons

• Cytokines produced by host cells (B & T lymphocytes) in response to viral infections. Now made by recombinant DNA technology

• Mechanism – suppression of viral protein synthesis

• Types – α, β, γ

• ADR – Neutropenia, tremor, hypotension, arrhythmias

• Uses – chronic hepatitis B, herpes zoster, common cold prophylaxis
Treatment of viral warts

• IFN α-2b or IFN α-n3 intralesional inj

• Podifloxor podophylline topical solution

• Imiquimod topical ointment
## Antiretroviral Agents

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Drugs</th>
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</thead>
<tbody>
<tr>
<td>Entry inhibitors or FIs</td>
<td>Enfuvirtide, maraviroc</td>
</tr>
<tr>
<td>NRTIs</td>
<td>Tenofovir, adebovir, zidovudine, didanosine, stavudine, emtricitabine, abacavir, lamivudine</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>Efavirenz, rilpivirine, nevirapine, dapivirine or etravirine</td>
</tr>
<tr>
<td>PIs</td>
<td>Ritonavir, darunavir</td>
</tr>
<tr>
<td>IIs</td>
<td>Dolutegravir, raltegravir</td>
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</table>

**Abbreviations:** FIs, fusion inhibitors; IIs, integrase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors.
Nucleoside/nucleotide RTIs – examples of adverse effects

All **NRTIs** can cause mitochondrial toxicity leading to lactic acidosis, hepatic steatosis, and hepatomegaly. Also nausea, vomiting, diarrhoea

- GI upset – nausea, vomiting, diarrhoea
- Headache (esp. AZT)
- Pancreatitis (esp. ddl, d4T)
- Peripheral neuropathy (esp. ddC, d4T)
- Renal toxicity (tenofovir)

**NNRTIs** can cause skin rash

- CNS effects (esp. efavirenz)
- Life-threatening hepatotoxicity (nevirapine)
COVID-19
COVID-19

• A single positive-sense RNA virus.

• Mutation rates of RNA viruses are greater than DNA viruses → more efficient adaptation process for survival.

• It uses its spike glycoprotein (S), a main target for neutralization antibody, to bind its receptor, and mediate membrane fusion and virus entry.

• Non-structural proteins include: orf1ab, ORF3a, ORF6, ORF7a, ORF10 and ORF8.

<table>
<thead>
<tr>
<th>Structural Protein</th>
<th>Function of Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleocapsid Protein (N)</td>
<td>Bound to RNA genome to make up nucleocapsid</td>
</tr>
<tr>
<td>Spike Protein (S)</td>
<td>Critical for binding of host cell receptors to facilitate entry of host cell</td>
</tr>
<tr>
<td>Envelope Protein (E)</td>
<td>Interacts with M to form viral envelope</td>
</tr>
<tr>
<td>Membrane Protein (M)</td>
<td>Central organiser of CoV assembly</td>
</tr>
<tr>
<td></td>
<td>Determines shape of viral envelope</td>
</tr>
</tbody>
</table>
Viral Load

• Peak at $7.11 \times 10^8$ RNA copies per throat swab

• Patients with severe COVID-19 tend to have a high viral load and long virus-shedding period.

• The mean viral load of severe cases was around 60 times higher than that of mild cases......

........suggesting that higher viral loads might be associated with severe clinical outcomes.
Pathogenesis

• Spike proteins, ORF8 and ORF3a proteins

• ORF8 and surface glycoprotein combine with porphyrin to form a complex

• orf1ab, ORF10, ORF3a attack the heme on the 1-beta chain of hemoglobin to dissociate the iron from the porphyrin.

• This inhibits the normal metabolic pathway of heme → less heme → inability to exchange carbon dioxide and oxygen → Respiratory distress
Frame Work for Prevention & Treatment:

Clinical Care Guidelines:

• Infection control and clinical management

• Additional guidelines for SARI, ARDS, sepsis

• Separate guidelines for:
  - testing
  - use of PPE
  - isolation and home isolation management
  - disinfection
  - waste disposal
Framework: Pre-Therapeutic

• **Confirmed case** – lab confirmed positive, irrespective of signs and symptoms

• **Categorization**: Mild illness, pneumonia, severe pneumonia, ARDS, Sepsis, Septic shock

• **Early triage and strict IPC measures**
  • **First point of contact**- patient given mask, single room with ventilation or at least 1m separation
  • **Contact precautions**- PPE while entering room, remove while leaving. Disposable/dedicated equipment (if not possible, disinfect in between)
  • **Airborne precautions** – in aerosol-generating procedures. Perform with full PPE, full-sleeve, eye protection, N95 masks that are fit-tested. Site precautions.

• **Lab diagnosis** – specimens – URT/LRT – collection and transport precautions
Framework: Management

- Management of SARI → ARDS → Sepsis → septic shock → MODS

- **Mild COVID 19:** only URTI, no pneumonia
  - Symptomatic treatment and monitoring
  - Anti-pyretics, isolation at home* after counselling (signs and symptoms of complications, prevention of transmission)

- **Severe COVID 19**
  - **Oxygen therapy:** all patients with respiratory distress – use high flow rate
  - **Fluid management:** conservative fluid management if no shock. Isotonic crystalloids only.
  - **Empiric antimicrobials:** within 1 hour of initial assessment in suspected sepsis- according to local epidemiology and treatment guidelines + Neuraminidase inhibitor. Subsequent de-escalation
  - **Steroids:** avoid high dose. Except for treatment of COPD, asthma exacerbation, septic shock, preterm labour
Framework: Management

❖ **Severe COVID 19**
  • Monitoring
  • Co-morbidities, other conditions:
    • **Hypertension**: continue medications – ACEI and ARBs also.
    • **Pregnancy**: similar to non-pregnant. No evidence of increased risk/adverse foetal outcomes. No vertical transmission, no transmission via milk. (WHO)
    • **Old age**: high risk
    • **Communication with patient and family**

❖ **Management of respiratory failure and ARDS**
❖ **Management of septic shock + Prevention of complications**
❖ **Specific therapy**: none approved
## A Snapshot of Guidelines

<table>
<thead>
<tr>
<th></th>
<th>Country</th>
<th>WHO</th>
<th>CDC</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background</strong></td>
<td></td>
<td>Percentage of illness of different severity, risk groups, risk factors for severe illness</td>
<td>+ Epidemiology in detail, symptoms, USA data Incubation periods in detail</td>
<td>Brief</td>
</tr>
<tr>
<td><strong>Screening, triage, management of mild COVID 19</strong></td>
<td>Detailed procedure for sample collection, advice nasal swab</td>
<td>Advice nasopharyngeal and oropharyngeal sample. Better yield expected from LRT sample. Avoid collection from nostrils. Describes management of mild illness.</td>
<td>Technical guidelines in detail</td>
<td></td>
</tr>
<tr>
<td><strong>Unique features</strong></td>
<td></td>
<td>Detailed description for pregnant, breast-feeding and older individuals Specialised guideline for sepsis and septic shock</td>
<td>Reinfection addressed – less likely based on current data. Discusses asymptomatic and pre-symptomatic stage; co-medications.</td>
<td></td>
</tr>
<tr>
<td><strong>Specific therapy</strong></td>
<td>HCQ prophylaxis for high risk</td>
<td>Refers reader to clinical trials, off label use mentioned briefly</td>
<td>Remdesivir HCQ and chloroquine</td>
<td>As per ICMR guidelines</td>
</tr>
</tbody>
</table>
WHO Interim Guidance

• There is no current evidence to recommend any specific anti-COVID-19 treatment for patients with confirmed COVID-19.

• There are many ongoing clinical trials testing various potential antivirals

• These are registered on https://clinicaltrials.gov/ or on the Chinese Clinical Trial Registry (http://www.chictr.org.cn/abouten.aspx).
WHO Solidarity Trial

- Adults (age ≥18 years) recently hospitalised, or already in hospital, with confirmed COVID-19 and with no contra-indication to any of the study treatments......

........... will be randomly allocated between:

- Local standard of care,
- OR local standard of care plus one of:
  1. Remdesivir
  2. Chloroquine or Hydroxychloroquine
  3. Lopinavir with Ritonavir
WHO Solidarity Trial

• The patients will be followed up for the entire length of their hospital stay.
• Death from any cause will be recorded and this will be the main result used to determine whether a drug is effective.
• Length of hospital stay and time to first receiving ventilation (or intensive care) will also be recorded and used to determine the drug's effectiveness.

• Underlying conditions recorded are: diabetes, heart disease, chronic lung disease, chronic liver disease and asthma, extending to HIV and tuberculosis in the African region.

• Severity of illness at entry is determined by recording: shortness of breath, being given oxygen, already on a ventilator, and if lungs imaged, major bilateral abnormality.
Hydroxychloroquine & Chloroquine

- Chloroquine and hydroxychloroquine - 4 aminoquinolines
- Chloroquine - used for malaria treatment and prophylaxis
- Hydroxychloroquine (HCQ) - used for treatment of rheumatoid arthritis, SLE
- Both have shown in-vitro activity against SARS-CoV, SARS-CoV-2
- Hydroxychloroquine having relatively higher potency against SARS-CoV-2
- A small study in China - chloroquine treatment of COVID-19 patients had clinical and virologic benefit versus a comparison group
- Based upon limited in-vitro and anecdotal data.....chloroquine or HCQ currently recommended for treatment of hospitalized COVID-19 patients in some countries
- Both chloroquine and HCQ have known safety profiles with main concerns being cardiotoxicity (prolonged QT syndrome) with prolonged use in patients especially with hepatic or renal dysfunction and immunosuppression
Chloroquine
Mechanism of action
Possible mechanism against Corona virus

Virus enter host cells through endocytosis.

virus transported within the host cell in a cell-membrane derived vesicle called an endosome, within which the virus can replicate.

When the endosome fuses with the acidic intracellular lysosome, this leads to rupture of the endosome with the release of the viral contents.

Eg: Chloroquine found to accumulate in lysosomes, interfering with this process, and may raise pH level of the endosome, which may interfere with virus entry and/or exit from host cells.
Adverse Effects of Hydroxychloroquine

Common ADR

• Nausea, Vomiting
• stomach pain or cramps
• Loss of appetite, Weight loss
• Diarrhoea
• Dizziness, Headache
• Ringing in your ears
• Mood changes
• Nervousness, Irritability,
• Skin rash or itching

Serious ADR

• muscle weakness, twitching
• uncontrolled movement
• loss of balance or coordination
• blurred vision
• seeing halos around lights
• Pale skin
• easy bruising or bleeding
• Confusion, unusual behavior
• Seizures
• Weak pulse and arrhythmias
Remdesivir

- Remdesivir is an intravenous drug with broad antiviral activity
- Originally developed to combat Ebola and related viruses,
- It shuts down viral replication by inhibiting a key viral enzyme, the RNA-dependent RNA polymerase
- Researchers tested remdesivir during the Ebola, along with three other treatments. It was not a success. But the enzyme it targets is similar in other viruses
- In 2017 researchers at UNC, showed in test tube and animal studies that the drug can inhibit coronavirus causing SARS and MERS
- The first COVID-19 patient diagnosed in US given remdesivir when his condition worsened; he improved the next day - case report in NEJM
- A Californian patient who received remdesivir—and who doctors thought might not survive - also recovered.
Other agents

Lopinavir + Ritonavir

• Licensed treatment for HIV

• Because lopinavir is broken down in body by our own proteases, it is given with low levels of ritonavir -lets lopinavir persist longer.

• Evidence for COVID-19, MERS and SARS is yet to show it can improve clinical outcomes or prevent infection.

• Studies done so far in COVID-19 patients have been inconclusive.

Interferon Beta – 1a

• Used to treat multiple sclerosis
What else do we know? – A sample

• Treatment for COVID-19 is primarily supportive care, including mechanical ventilation and antibiotics to prevent secondary infection as appropriate.

• Preliminary reports from two clinical trials in China suggest that favipiravir improves lung function and reduces recovery time in COVID-19 patients.

• Early results suggest that tocilizumab may be effective at treating severe COVID-19 cases.

• A small clinical trial suggest that chloroquine is effective at reducing symptom duration.
What do we need to know? – a sample

- Is GS-5734 (remdesivir) effective in vivo (already used in clinical trials under Emergency Use Authorization)?
- Is the GLS-5000 MERS vaccine cross-reactive against SARS-CoV-2?
- Efficacy of antibody treatments developed for SARS and MERS?
- What is the efficacy of various MERS and SARS Phase I/II vaccines and other therapeutics?
- Are viral replicase inhibitors such as beta-D-N4-hydroxycytidine effective against SARS-CoV-2?
- What about Ivermectin, since invtro it has shown good efficacy in vitro?
Ongoing, just starting studies....plenty!

- Viriom (CA, USA) initiates Phase II clinical trial of elsulfavirine for treatment of moderate COVID-19
- MediciNova (CA, USA) announces plans to initiate a clinical trial of MN-166 (ibudilast) for COVID-19 acute respiratory distress syndrome
- Chugai (Tokyo, Japan) starts Phase III clinical trial of monoclonal antibody treatment Actemra for COVID-19 pneumonia
- Novant Health (NC, USA) starts Phase II COVID-19 trial testing CytoDyn’s (WA, USA) leronlimab
- Oral antiviral EIDD-2801 shows promising preclinical results against COVID-19
- FDA approves Investigational New Drug application, allowing Ridgeback Biotherapeutics (FL, USA) to begin human testing of EIDD-2801, a potential treatment for COVID-19
- Kedrion Biopharma (Lucca, Italy) announces initiation of the development of a plasma-based therapy for treating COVID-19
Ongoing, just starting studies...a plenty!

- Ennaid Therapeutics (GA, USA) announces development of ENU200, a novel antiviral therapeutic, for the treatment of COVID-19
- University Hospital Basel (Switzerland) transfuses first two COVID-19 patients with INTERCEPT-treated coronavirus convalescent plasma
- PharmaMar (Madrid, Spain) submits a Phase II clinical trial protocol of plitidepsin for the treatment of COVID-19 to the Spanish Medicines Agency
- Vanda Pharmaceuticals (WA, USA) announces the initiation of ODYSSEY, an FDA-approved Phase III clinical study of tradipitant in hospitalized patients with Severe COVID-19 pneumonia
- Incyte (DE, USA) and Novartis (Basel, Switzerland) to initiate a Phase III study testing ruxolitinib for severe COVID-19 patients
- Celltrion’s (Incheon, South Korea) COVID-19 antiviral treatment enters the second phase of development
Ongoing, just starting studies….plenty!

- Anti-parasitic drug ivermectin kills COVID-19 in Monash Biomedicine Discovery Institute (Victoria, Australia) lab
- I-Mab (China) announces FDA clearance of Investigational New Drug application (IND) to initiate clinical study for TJM2 to treat cytokine release syndrome (CRS) associated with COVID-19
- Cytovia Therapeutics (NY, USA) and Macromoltek (TX, USA) to develop natural killer immunotherapy against SARS-CoV-2
- Mateon (CA, USA) expands its COVID-19 therapeutic program to include anti-malarial drug Artemisinin
- The Vector Institute (Kol’tsovo, Russia) announces plans to start clinical trials for coronavirus in June
- Queen’s University (Belfast, UK) leading cell therapy clinical trial to help improve outcomes in COVID-19 patients
- The Montreal Heart Institute (Canada) announces partnership with the NYU Grossman School of Medicine (NY, USA) for its COVID-19 clinical study evaluating colchicine for preventing major inflammatory storm
Vaccines – a hope?

• The two vaccines which are in Phase 1 are from CanSino Biological Inc. and Beijing Institute of Biotechnology; and Moderna/the National Institute of Allergy and Infectious Disease (NIAID) in the US.

• Flow Pharma (CA, USA) announces initiation of pre-clinical study to test efficacy of FlowVax COVID-19 vaccine

• Oxford Biomedica (UK) joins Consortium to rapidly develop a COVID-19 vaccine candidate, ChAdOx1 nCov-19

• Serum Institute of India (Pune, India) currently testing two COVID-19 vaccine candidates in preclinical trials

• Flinders University (Adelaide, Australia) begins testing of COVID-19 vaccine candidate

• The role of BCG?
The horizon – a challenge

- Viral treatment – a challenge
- COVID 19 – even more of a challenge
- A medical, economic and humanitarian crisis
- Self isolation, quarantine, hygiene, PPE all crucial
- Anti-viral treatment – weak evidence, but clinical trials ongoing
- Vaccine – will take time
- Other challenges include inadequate health infrastructure & suboptimal health systems

“For humanity – it’s a challenge...real and true, but by working together, we can get through, by thinking together, we can break through!” – Sujith J Chandy
Thank You