Model-informed Drug Repurposing: Applications for COVID-19

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Our Panelists

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CEO of Pharmacometrics Africa and CP+ Associates, both social ventures that develop scientific capability in drug discovery & development in LMIC.

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Senior Director of Integrated Drug Development at Certara  
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Director of Integrated Drug Development at Certara  
Focused on PKPD modeling, clinical trial simulations & systems pharmacology.

**Michael Dodds**  
Executive Director of Integrated Drug Development at Certara  
15 years of drug development experience, applying pharmacometrics with an emphasis on decision quality and business impact.
Agenda

• Introduction
• Overview of Model-Informed Drug Repurposing
• Compound Screening
• In Silico Workbench and Examples
• Q&A
Housekeeping

- Please use the Zoom Q&A feature to post your questions and these will be addressed during the Q&A session at the end. You can also send in any questions you have after the session by going to the forums at covidpharmacology.com.

- Today’s webinar will be available on demand after the live session and will be posted on Pharmacometrics Africa website (www.pmxafrica.org), along with all the resources that will be shared.

- You can share today’s webinar with your social networks on Twitter, Facebook, or LinkedIn once you get access to the webinar recording.
Flatten the curve to the healthcare system capacity

https://africacdc.org/covid-19/
Clinical research for COVID is accelerating
Can we transition from chaos to co-ordination?

- [https://www.therapeuticsaccelerator.org/](https://www.therapeuticsaccelerator.org/)
- [https://covid19crc.org/](https://covid19crc.org/)
- [www.covidpharmacology.com](http://www.covidpharmacology.com)

Type in any other collaboration groups into the chat box
Pharmacometrics
Quantitative analysis of interactions between drugs and patients, with a focus on populations and variability

Pharmacometrics:
the science of developing and applying mathematical and statistical models to characterize, understand and predict a drug's pharmacokinetics, pharmacodynamics and biomarker-outcome behavior covering beneficial and adverse effects

Pharmacokinetics (PK) “what the body does to the drug”
Pharmacodynamics (PD) “what the drug does to the body”
Biomarker - outcome systems pharmacology, physiology, disease progression, biomarkers and clinical endpoints

All things are poison... it all depends on the dose

"All things are poison, and nothing is without poison; only the dose permits something not to be poisonous.” Paracelsus (1493-1541)

It's all about Dose-Response...

Get the right dose to the right patient

Slides from www.pmxafrica.org/learn
Measure drug concentrations to study pharmacokinetics

- **Cmax**: Maximum plasma concentration.
- **AUC**: Area under the curve.
- **Cavg**: Average plasma concentration.
  \[ C_{avg} = \frac{AUC}{dosing\ interval} \]
- **Cmin**: Minimum plasma concentration.
Use a mathematical model to explore dose regimens

\[ C = \frac{k_a \cdot D}{V(k_a - k_e)} \left( e^{-k_e \cdot \text{time}} - e^{-k_a \cdot \text{time}} \right) \]
Find dose regimens within the therapeutic window

Emax

\[ \text{Effect} \]

\[ \text{Conc} \]

\[ \text{EC}_{50} \]

\[ \text{Log Concentration - Effect / Adverse Effect} \]

\[ 0.1 \quad 1.0 \quad 10.0 \quad 100.0 \quad 1000.0 \quad 10000.0 \]

\[ 0 \quad 20 \quad 40 \quad 60 \quad 80 \quad 100 \]

\[ 0.01 \quad 0.1 \quad 1 \quad 10 \quad 100 \quad 1000 \quad 10000 \]
Success with a therapy needs multiple contributors

**Pharmacokinetics**
- Formulation
- Absorption
- Distribution
- Metabolism
- Elimination

**Pharmacodynamics**
- Drug-receptor interaction
- Biosensor Process
- Transduction
- Biomarkers
- Efficacy Endpoints
- Safety Readouts

**Influencing Factors**
- Intrinsic vs Extrinsic factors
- Demographics
- Patho-physiology
- Treatment Duration / Combinations
COVID-19 has several potential “druggable” targets

ACE2, angiotensin-converting enzyme 2; S protein, spike protein; and TMPRSS2, type 2 transmembrane serine protease

https://doi.org/10.1016/
Model-Informed Drug Repurposing: Overview

• In the context of a novel pathogen such as SARS-CoV-2, repurposing existing drugs offers the promise of a rapid treatment response to COVID-19 while more specific treatments are developed.

• Model-informed drug repurposing (MIDR) approaches are thought of in the same sense as model-informed drug development.

MIDR: the application of a wide range of quantitative tools in drug repurposing to facilitate prioritization and decision-making

• Think of the process as a filter or a method by which we can prioritize precious resources
  o Time, Patients-at-Risk

• The closest analogue to traditional drug-development is an oncology indication where there is poor SoC
  o Risk-benefit, Adaptation
Establish a Therapeutics Clearinghouse for COVID-19

Based on rapidly emerging information on COVID-19 virus/host characteristics, how can we “prioritise” candidate therapeutics, and “predict” their optimal dose that is credible to those that advise on antiviral use in a pandemic?

Establish a scientific fact base and triaging process to accelerate therapeutic interventions trials for COVID19

Focus on Convergence

Translational Pharmacology Roadmap

(Triaging Strategy)

Proof of Hope

Pharmacological Plausibility

Proof of Concept

Clinical Application & Continued Posology Optimization

Examples:

Hydroxychloroquine PEP
Lopinavir/ritonavir early Rx
Ivermectin
Example: Mapping MIDD (Seasonal flu) to MIDR (novel Pandemic flu)

Translational Pharmacology Strategy: “The First Roadmap”

MIDR
- Novel influenza strain
- Strategic drivers
- In vitro virology
- In vivo virology
- Pre-clinical
- Anecdotal clinical data
- Clinical trials
- Approval/Dosing Recommendation

MIDD
- Seasonal influenza
- Strategic drivers
- In vitro virology
- In vivo virology
- Pre-clinical
- Phase I/II
- Phase III
- Approval/Dosing Recommendation
**MIDR: Approach Overview**

- **in vitro + Label**
  - Label IC\(_{50}\) > CoV IC\(_{50}\)?
  - Clinical C\(_{ss,avg}\) > CoV IC\(_{50}\)?

- **in vitro + PK**
  - C(t) at SOA > CoV IC\(_{50}\)?
  - Adjust posology: loading dose, special populations?

- **Clinical PK + virology**
  - C(t) at SOA impact on VK?
  - What are the PK predictors of VD?

- **Clinical PK + outcome**
  - Exposure-response relationship?
  - Is disease a special population?

- **MBMA**
  - Can heterogeneous study designs add value?
  - How to address evolving SoC, populations, ..?
Compound Screening Dashboard
covidpharmacology.com
In Vitro + Label: “proof of hope”

Label IC$_{50}$ > CoV IC$_{50}$?

- It is likely that the drug is dosed to achieve concentrations above effective thresholds in the original indication.
- However, there is unlikely to be a 10x (or more) difference in effective and toxic doses.
- Thus, if an effective concentration against CoV is orders-of-magnitude higher than the effective concentration in the label, it is unlikely we can achieve those concentrations without safety issues.

CSS,avg > CoV IC$_{50}$?

- Relatively minimal ADME information (CL, fu) is required to calculate CSS,avg at the labeled posology.
- However, there is unlikely to be a 10x (or more) difference in effective and toxic doses.
- If that concentration is orders-of-magnitude lower than the effective concentrations against CoV, it is unlikely we can achieve those concentrations without safety issues.

We do not reject a compound with these tools; we prioritize. We maintain a ranked priority list for further development.
In Vitro + Label: “proof of hope”

Plasma concentration mg/L

Time h

0 5 10 15 20 25 30

CoV IC50

Label IC50

Cavg

CoV IC50
Call to a collaborative and efficient R&D

Given the large costs and slow pace of the development of new drugs, repurposing of drugs to treat other diseases is an attractive option. The use of well-studied compounds will potentially shorten the development timelines considerably.

R&D's ROLE IN A PANDEMIC
Developing New Tools in Response to COVID-19

FOCUS ON THE DEVELOPMENT OF DIAGNOSTICS:
SHORT-TERM: Develop public health surveillance tools, using molecular diagnostics to detect cases for treatment and isolation.
LONG-TERM: Develop point-of-care diagnostics for use by health workers.

IDENTIFY AND DEVELOP THERAPIES THAT ARE:
• Safe in humans
• Active against COVID-19
• Quickly manufactured in hundreds of millions of doses
• Deliverable in low-resource settings

IDENTIFY POTENTIAL VACCINES AND MONOCLONAL ANTIBODIES THAT ARE:
• High efficacy for community protection
• Safe in humans
• Active against COVID-19
• Quickly manufactured in hundreds of millions, if not billions, of doses
• Deliverable in low-resource settings

COLLABORATIONS:
Multiple partners
COVID-19 Therapeutics Accelerator
CEPI

https://www.gatesfoundation.org/TheOptimist/Articles/coronavirus-mark-suzman-therapeutics
Based on rapidly emerging information on COVID-19 virus/host characteristics, how can we “prioritise” candidate therapeutics, and “predict” their optimal dose that is credible to those that advise on antiviral use in a pandemic?

Establish a scientific fact base and triaging process to accelerate therapeutic interventions trials for COVID19

Focus on Convergence

PK/PD
In vitro & In vivo Models
Virus/Host Biomarkers
Clinical & Immunology
Epidemiology Modelling
VK Models

In Silico Workbench

Translational Pharmacology Roadmap

(Triaging Strategy)

Proof of Concept
Pharmacological Plausibility
Proof of Hope

Clinical Application & Continued Posology Optimization

Triaging Strategy

We aim to establish a scientific fact based and triaging process to accelerate therapeutic interventions trials for COVID-19.

Background

No drugs/vaccines/therapeutics are currently approved to prevent or treat COVID-19. Current clinical management includes infection prevention and control measures and supportive care, including supplemental oxygen and mechanical ventilatory support when indicated (CDC 2020) [https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html]

Several investigational therapeutics options can be considered: vaccines, monoclonal antibodies, oligonucleotide-based therapies, peptides, interferon therapies and small-molecule drugs. However, completely new therapeutics options will require months to years of development. On the other hand, therapies that are currently on the market, or are at the late stages of development, can be made available quickly. (Baric and Spear 2019; Flavon and Lednicky 2017; Machen and Opal 2019; Antinori et al. 2020; Li and De Clercq 2020; and Al-Sabawi&Choi&PharmacyTimes2020).
### Filter for compounds by Name

#### Table Filters

- **Chloroquine**
- **Hydroxychloroquine**
- **Favipiravir**
- **Lopinavir**
- **Ritonavir**
- **Ribavirin**
- **Nattoside**
- **Nitazoxamide**
- **Camostat**
- **Nafamostat**
- **Leffarnamide**
- **Netamivir**
- **Teicoplanin**
- **Eboceprevir**
- **Digoxin**
- **Danarnir**
- **Azithromycin**
- **Ivermectin**
- **Remdesivir**
- **Lofaradin**
- **Tocilizumab**
- **Interferon Beta-2a**
- **Apremilast**

#### Compounds Table

<table>
<thead>
<tr>
<th>Compound</th>
<th>MOA</th>
<th>Mtr</th>
<th>Indication</th>
<th>Class</th>
<th>MW_g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine</td>
<td>antimalarial</td>
<td></td>
<td></td>
<td></td>
<td>320</td>
</tr>
<tr>
<td>Hydroxyclor</td>
<td>immune modulator</td>
<td></td>
<td></td>
<td></td>
<td>336</td>
</tr>
<tr>
<td>Favipiravir</td>
<td>anti-viral</td>
<td></td>
<td>Flu</td>
<td></td>
<td>157</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>anti-viral</td>
<td></td>
<td></td>
<td></td>
<td>244</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>anti-hepatic</td>
<td></td>
<td></td>
<td></td>
<td>527</td>
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<tr>
<td>Ribavirin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>307</td>
</tr>
<tr>
<td>Nattoside</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>875</td>
</tr>
</tbody>
</table>

#### Heatmap Controls

- **Metric to Color Heatmap:**
  - Mean of
  - Ratio Metrics
- **Heatmap Compound Ordering:**
  - Good on Top
  - Worst
- **Color Scale:**
  - Red
  - Yellow
  - Green
  - Blue

Select at least one Compound row.
### Compounds Table

#### Table Filters

**Filter by Mechanism of Action**

Select Rows of Compounds of Interest

- **Compound**
- **Status**
- **Purpose**
- **MOA**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Status</th>
<th>Purpose</th>
<th>MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine</td>
<td>approved</td>
<td>virus kill</td>
<td>antimalarial</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>approved</td>
<td>virus kill</td>
<td>immune modulator</td>
</tr>
<tr>
<td>Favipiravir</td>
<td>approved</td>
<td>virus kill</td>
<td>anti-viral</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>approved</td>
<td>virus kill</td>
<td>anti-viral</td>
</tr>
<tr>
<td>Niclosamide</td>
<td>approved</td>
<td>virus kill</td>
<td>anti-helminthic</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>approved</td>
<td>virus kill</td>
<td>anti-viral</td>
</tr>
<tr>
<td>Ivermectin</td>
<td>approved</td>
<td>virus kill</td>
<td>Anti-parasitic</td>
</tr>
</tbody>
</table>

**Select All**

**Select at least one Compound row**

Showing 1 to 7 of 7 entries

### Heatmap

**Heatmap Controls**

- **Heatmap Compound Ordering:**
  - Good on Top
  - Visibly

- **Color Scale:**

Select one Compound row
Explore the properties and Select those of Interest or just select all

An interactive heat map with user chosen sorting
Sort by the metric of choice
Several ordering options
### Compounds Table

#### Table Filters
- Compounds: Chloroquine, Hydroxychloroquine, Favipiravir
- Mechanism of Action (MOA): antimalarial, immune modulator, anti-viral

#### Select Rows of Compounds of Interest
- Note: Hold `ctr`, (Windows) or `cmd`, (Mac) to select multiple rows at once.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Status</th>
<th>Purpose</th>
<th>MOA</th>
<th>MOA Class</th>
<th>MW_dg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine</td>
<td>approved</td>
<td>virus kill</td>
<td>antimalarial</td>
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<tr>
<td>Hydroxychloroquine</td>
<td>approved</td>
<td>virus kill</td>
<td>immune modulator</td>
<td>RA</td>
<td>200</td>
</tr>
<tr>
<td>Favipiravir</td>
<td>approved</td>
<td>anti-viral</td>
<td>Flu</td>
<td>direct anti viral</td>
<td>150</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>approved</td>
<td>virus kill</td>
<td>antiviral</td>
<td>Reoche</td>
<td>240</td>
</tr>
<tr>
<td>Niclosamide</td>
<td>approved</td>
<td>virus kill</td>
<td>anti-helminthic</td>
<td>Bayer</td>
<td>320</td>
</tr>
<tr>
<td>Nitazoxanide</td>
<td>approved</td>
<td>virus kill</td>
<td>antiparasitic</td>
<td>Remark</td>
<td>320</td>
</tr>
<tr>
<td>Ivermectin</td>
<td>approved</td>
<td>virus kill</td>
<td>Anti-parasitic</td>
<td>Merck</td>
<td>875</td>
</tr>
</tbody>
</table>

Showing 1 to 7 of 7 entries - 7 rows selected

### Heatmap

#### Heatmap Controls
- Metric to Color Heatmap:
  - Mean of Ratio Metrics
  - Ratio: Cmax/EC50
  - Ratio: Cmax/C50
  - Ratio: PK/EC50
- Heatmap Compound Ordering:
  - Bad on Top
- Color Scale:
  - Excel
  - Color Blind
  - Virids

#### Heatmap Table
- Score:
  - g: good
  - b: medium
  - m: bad
  - d: No Info

Several coloring options
Zoom to the “good” region + hover for additional info
Additional clin pharm info in the table
### Azithromycin

**General Information**

- Oral tablets: 250 mg and 500 mg
- Oral suspension: 100 mg/5mL and 200 mg/5mL
- Extended release oral suspension: 27 mg/mL (discontinued)
- Injection: 500 mg/vial and 1 g/vial
- Oral capsule: 250 mg (discontinued)

- Binding to the 50S ribosomal subunit of susceptible microorganisms inhibiting bacterial protein synthesis and impeding the assembly of the 50S ribosomal subunit.

**Proven in Vito and/or Clinically Proven in Vito only**

<table>
<thead>
<tr>
<th>Haemophilus influenzae</th>
<th>Hemolytic streptococci (Groups A and C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moraxella catarrhalis</td>
<td>Viridans group streptococci</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Bordetella pertussis</td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td>Legionella pneumophila</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>Pneumocystis jiroveci</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>Peptostreptococcus species</td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
<td>Ureaplasma urealyticum</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>N/A</td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td>N/A</td>
</tr>
</tbody>
</table>

### Potential mechanism of action in COVID-19

- Inhibition of viral replication and IL-6 production

### Administration and Adverse Events

**Adverse Events**

- **Adults**
  - Community-acquired pneumonia, pharyngitis/folliculitis: 500 mg OD on Day 1, followed by 250 mg OD, Days 2 through 5
  - Chronic bronchitis: 500 mg OD on Day 1, followed by 250 mg OD, Days 2 through 5 or 500 mg QD for 3 days
  - Sinusitis: 500 mg OD for 3 days
  - Genital ulcer disease, non-gonococcal urethritis and cervicitis: 1 g SD
  - Gonococcal urethritis and cervicitis: 2 g SD

**Pediatric Patients**

- Acute otitis media (6 months and older): 30 mg/kg OD or 10 mg/kg QD for 3 days or 10 mg/kg OD Day 1 followed by 5 mg/kg Days 2 through 5
- Acute bacterial sinusitis (6 months and older): 10 mg/kg OD for 3 days
- Community-acquired pneumonia (6 months and older): 10 mg/kg OD Day 1, followed by 5 mg/kg OD Days 2 through 5
- Pharyngitis/folliculitis (2 years and older): 12 mg/kg OD for 5 days
- Pharyngitis/folliculitis (1 year and younger): 25 mg/kg OD for 5 days

**Therapeutic dose and exposure as antibiotic**

**Therapeutic dose and exposure being evaluated in COVID-19 clinical studies**

- 500 mg OD for 5 days in addition to Hydroxychloroquine
- 500 mg OD Day 1 and 250 mg OD Days 2 to 7 (up to 10 days)
- 500 mg OD for 10 days in addition to Hydroxychloroquine
- 500 mg OD for 3 days
In Silico Workbench
covidpharmacology.com
Generally, we have available PK models for *repurposed* drugs. They come in two flavors:

1. popPK
   - *Pro*: between-subject variability; major exposure covariates; broadly implementable
   - *Con*: lacks site of action concentration predictions
2. PBPK
   - *Pro*: good handling of tissues/sites; special populations (pediatrics, geriatrics, etc.)
   - *Con*: complex to export to external software simulation framework

Each of these can be *flexed* to get a reasonable approximation to our critical question:

- **What is the dose-exposure relationship of this repurposed drug at a relevant site of action, and how does that compare to *in vitro* values that are thought to inhibit SARS-CoV-2?**

1. popPK: add unbound fraction calculation; add tissue: blood observations; add tissue: blood theoreticals
2. PBPK: bracket covariates with simulations and interpolate; use superposition of single-dose simulations to simulate different posologies, if applicable
In Silico Workbench: platform for early posology assessment and study design aid

Entry through COVID-19 Pharmacology Resource Center

Current inventory of our *in silico* workbench

https://www.covidpharmacology.com/in-silico-workbench/
Simulated concentration time profiles were compared with *in vitro* targets from various sources.

Options to select an established regimen from labels or literature.
Alternative dosing regimens can be explored and compared against *in vitro* targets.

Customized inputs provide flexibility to investigate “What if” scenarios.
For each target, PD simulations provide how much “buffer” we are expecting.
In Silico Workbench: Chloroquine

covidpharmacology.com
In Vitro + PK: Chloroquine

- Chloroquine (CQ) has been extensively used in treating malaria and some autoimmune disorders since 1940s, and is considered to have antiviral effects

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Malaria - FDA</td>
<td>1000 mg (600 mg base) PO, then 500 mg (300 mg base) PO 8-8 hours later, then 500 mg (300 mg base) PO at 24 and 48 hours</td>
</tr>
<tr>
<td>Acute Malaria - WHO</td>
<td>10 mg base/kg bw, then 10 mg base/kg bw at 24 hours, then 5 mg base/kg bw at 48 hours (assuming body weight 75 kg)</td>
</tr>
<tr>
<td>Malaria Suppression - FDA</td>
<td>500 mg (300 mg base) weekly (assuming 8 weeks of dosing)</td>
</tr>
</tbody>
</table>

- Azithromycin, believed to suppress airway inflammations, has been used since 1980s
- **Adverse cardiac events** noticed for both CQ and azithromycin when used separately, in particular in patients with a pre-existing heard condition
  - High dose CQ (600mg CQ twice daily for 10 days or total dose 12g)
  - Low dose CQ (450mg for 5 days, twice daily only on the first day, or total dose 2.7g)
  - In addition, all patients received ceftriaxone and azithromycin
In Vitro + PK: Chloroquine – toxicity concerns

3x C\textsubscript{max} relative to acute malaria exposure


Y Xiong, D Wesche, Karen Y
In Vitro + PK: Chloroquine – toxicity concerns

• CloroCovid-19 preliminary findings
  o Out of a pre-defined 440 patients sample size, 81 patients were enrolled
  o The high dose CQ arm presented more QTc>500ms (25%), and a trend toward higher lethality (17%) than the lower dosage.
  o Fatality rate was 13.5% (95%CI=6.9–23.0%), overlapping with the CI of historical data from similar patients not using CQ (95%CI=14.5-19.2%).

• These findings suggest that the higher CQ dosage (600 mg BID 10-day regimen) should not be recommended for COVID-19 treatment because of its potential safety hazards.

Also see Savic 2020
In Silico Workbench: Lopinavir / ritonavir
covidpharmacology.com
In Vitro + PK: Lopinavir / ritonavir

• KALETRA® (lopinavir/ritonavir)
  o Approved and used for the treatment and prevention of HIV/AIDS
  o Antiviral effect mainly through ritonavir boosted lopinavir, one of the protease inhibitors that are believed to prevent virus replication

• For HIV treatment, often used over a relatively long period of time
  o Approval based on studies of 72-week treatment duration

• For acute virus infection such as COVID-19, antivirals are often effective only if antiviral treatment is initiated early on after infection
  o Important to push exposure as high and as early as possible
In Vitro + PK: Lopinavir / ritonavir – importance of loading

400 mg BID, without loading
- Reaches target on Day 2
- Stays above for <2 days

400 mg BID, with Q6h loading
- Reaches target on Day 1
- Stays above for >3 days

In Silico Workbench: Ivermectin
covidpharmacology.com
In Vitro + PK: Ivermectin

• Ivermectin is extensively used for 5 neglected tropical diseases at single oral doses of 150 to 200 μg/kg.

• Recently Caly et.al reported that "The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro". In this study, ivermectin was found to inhibit the replication of SARS-CoV-2 in cells in Vero-hSLAM cells with an IC50 at approximately 2 μM.

• The assumption is that, since the drug is FDA-approved, it would readily translate into a treatment or cure for COVID-19. However, The question that was left unanswered was whether a single dose of 150 to 200 μg/kg could result in adequate amounts in a human body to inhibit replication of SARS-CoV-2 in the blood or the lungs.

• Preliminary findings suggest that standard doses of ivermectin would not result in efficacious concentrations, and that extraordinary doses to achieve efficacious concentrations may result in unacceptable toxicity in COVID-19 patients.

Also see: Bray 2020, Chaccour 2020, Momekov 2020, and warning by FDA
**In Vitro + PK: Ivermectin**

**AusPar (classic/typical scabies):**
200 μg/kg on Day 1 and another dose between Day 8 and Day 15

**WHO (onchocerciasis):**
150 μg/kg once yearly

**IVERMAL (mosquitocidal):**
600 μg/kg once daily for 3 days

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Y Xiong, Karen Y, D Wesche
https://www.covidpharmacology.com/in-silico-workbench
Questions?