A Clinician's Perspective On What Additional Data Should Be Collected On The Available Therapeutics?

Monkeypox Research: What are the knowledge gaps and priority research questions?
WHO Global Consultation
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Some Key Considerations

1. **Diagnostics**
2. **Virology**
3. **Define Clinical Spectrum**
    1. Spectrum of illness
    2. Natural history of illness
    3. Route of transmission
4. **Innovate of study designs**
    1. End-point development
        - Change over time?
    2. Platform trials, randomization frames, across resourced environments
    3. Regulator engagement
5. Prevention
    1. Pre-exposure
    2. Post-exposure
6. Treatment
    1. Pre-symptomatic
    2. Early illness
    3. Severe illness
7. Global Cooperation
    1. And communication

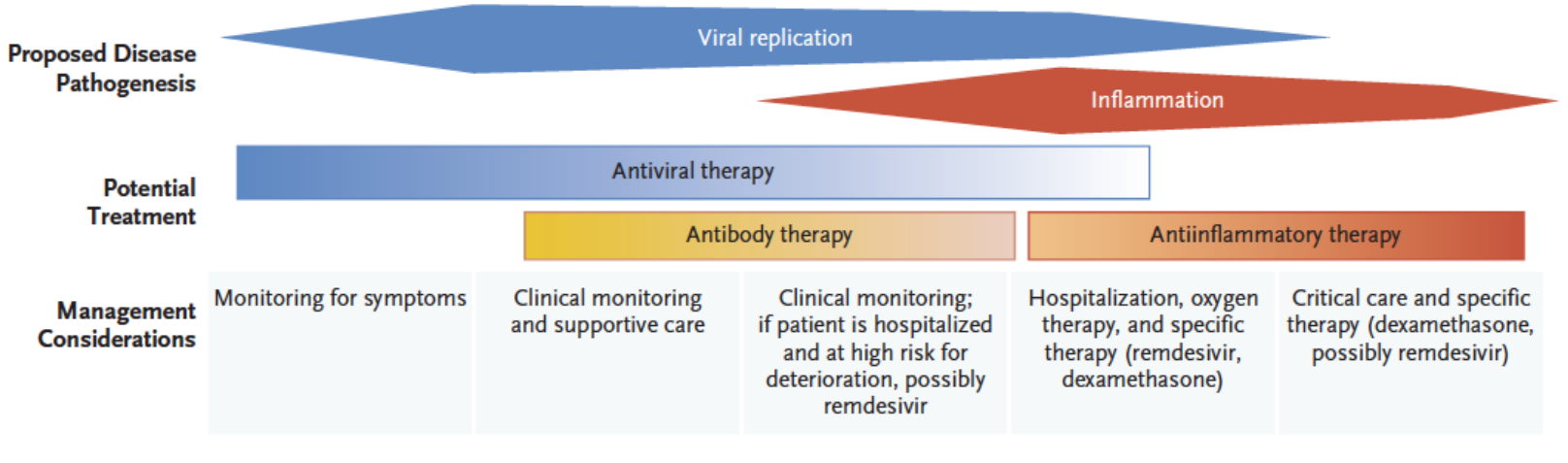
Timing and Pathogenesis

Pre-exposure Prophylaxis

Post-exposure Prophylaxis

Early Treatment **Later Treatment**

	Asymptomatic or Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical Illness
Features	Positive SARS-CoV-2 test; no symptoms	Mild symptoms (e.g., fever, cough, or change in taste or smell); no dyspnea	Clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation ≥94%	Oxygen saturation <94%; respiratory rate ≥30 breaths/min; lung infiltrates >50%	Respiratory failure, shock, and multiorgan dysfunction or failure
Testing	Screening testing; if patient has known exposure, diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing
Isolation	Yes	Yes	Yes	Yes	Yes



	Asymptomatic or Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical Illness
Management Considerations	Monitoring for symptoms	Clinical monitoring and supportive care	Clinical monitoring; if patient is hospitalized and at high risk for deterioration, possibly remdesivir	Hospitalization, oxygen therapy, and specific therapy (remdesivir, dexamethasone)	Critical care and specific therapy (dexamethasone, possibly remdesivir)

Figure 1. Characteristics, Diagnosis, and Management of Covid-19 According to Disease Stage or Severity.

Gandhi R NEJM 2020;383;18 1757-66
Epub April 24, print pub Oct 29, 2020

End Point Determination

- Define clinical syndrome
  - Natural history of illness
  - Impact route of transmission
- Easy access to high quality diagnostics
  - Viral culture, viral load/molecular testing (by compartment), serology
- What benefit do we want
  - Prevent severe illness
  - Mild/moderate illness
  - Transmission
- Correlate of Protection (CoP) or at least a Surrogate
  - Drug level, immune parameter

Biomarkers – On The "Take"

HIV Viral Load

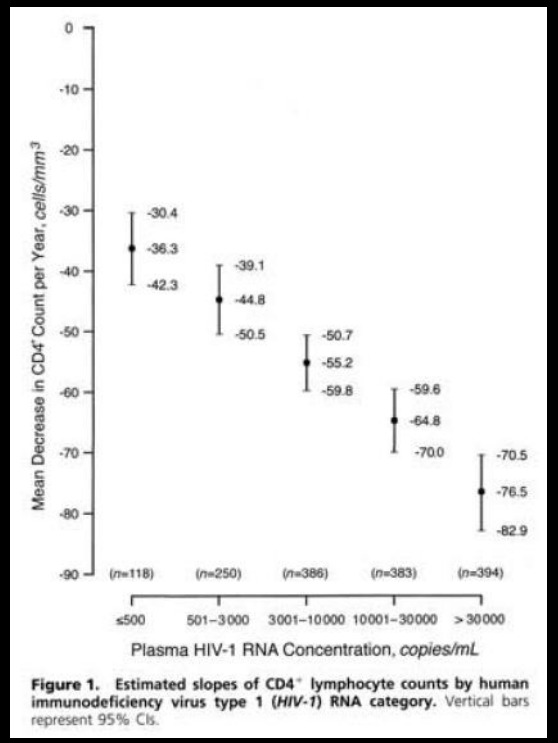


Figure 1. Estimated slopes of CD4+ lymphocyte counts by human immunodeficiency virus type 1 (*HIV-1*) RNA category. Vertical bars represent 95% CIs.

Mellors JW *Ann Int Med* 1997;126:946-54

The 'Take' (Vaccinia)

Table 1. Cutaneous Responses to Dryvax Challenge in Modified Vaccinia Ankara (MVA)–Vaccinated Groups

Group	MVA regimen[a]	No. of subjects (n = 36)	No. with Attenuated response	No. with Unattenuated response	P^b
A	1×10^6 ID	2	0	2	NA
B	1×10^7 IM	5	5	0	.001
C	1×10^7 SC	7	4	3	.07
D	1×10^8 SC	6	4	2	.02
E	1×10^7 ID	9	8	1	.001
Placebo	…	7	0	7	…

Category 1 **Category 2** **Category 3**

Seaman M et al, JID 2010:201(9):1353-60
Pittman PR NEJM 2019;381:1897-908

Potential Therapies: Integrate Several Lines of Evidence

- Vaccine (MVA/Vaccinia)
  - Pre and Post-exposure
- Tecovirimat (ST-246, TPOXX)
- Brincidofovir (CMX001) and cidofovir
- Immune globulin
  - Vaccinia immune globulin (VIG)

- *in vitro* activity
- Animal models
- PK/PD
- Clinical safety data
- **Clinical efficacy data**
  - Tempo of availability

ORIGINAL ARTICLE

Oral Tecovirimat for the Treatment of Smallpox

Douglas W. Grosenbach, Ph.D., Kady Honeychurch, Ph.D., Eric A. Rose, M.D., Jarasvech Chinsangaram, D.V.M., Ph.D., Annie Frimm, B.S., Biswajit Maiti, Ph.D., Candace Lovejoy, B.S., Ingrid Meara, M.S., Paul Long, B.S., and Dennis E. Hruby, Ph.D.

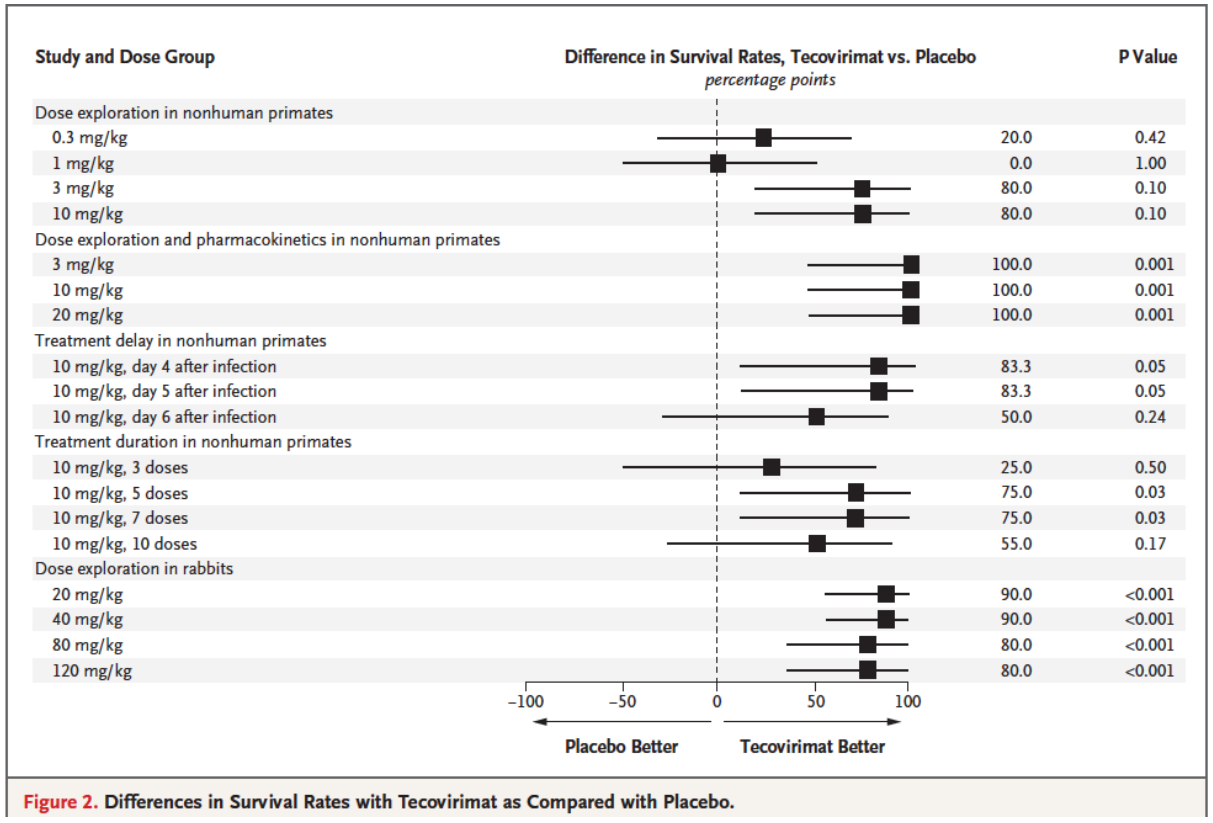


Figure 2. Differences in Survival Rates with Tecovirimat as Compared with Placebo.

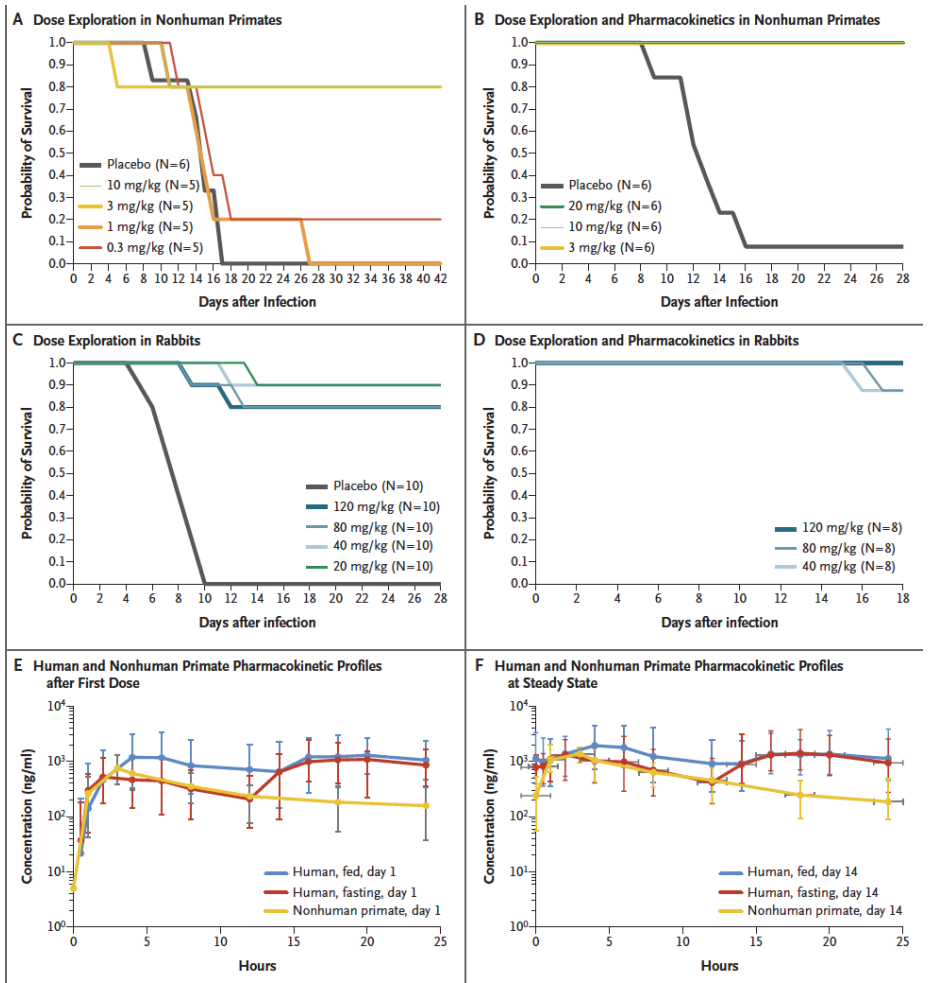


Figure 1. Efficacy and Pharmacokinetic Profiles of Tecovirimat in Animal Models.

Considerations

- Diagnostics
  - Speed, accuracy, portability, cost
- Natural history of illness
  - Beware of the anecdote
- Efficacy data
  - Properly controlled studies with innovative designs
- Timing of therapy
  - PrEP, PEP, early and later treatment
- Host factors
  - Impact prior orthopoxvirus immunity, specific health risk factors, immunocompetence
- Determination of an appropriate endpoint of value
  - Clinical improvement, abrogation of transmission
  - Development of a CoP

Considerations

- Special populations
  - Safety in pregnancy
  - Efficacy in immunocompromised patients (?prolonged infection)
- Compartment behavior
  - Both for the virus and countermeasures
  - Mucosal, prostate/semen
- Viral factors
  - Clade/strain, alterations in virulence, emergence of anti-viral resistance
- Globally organized studies
  - Equity of access, generalizability, speed
  - Enhance local capacity
- Manage communication
  - Challenge of real time data sharing globally