

Respiratory Viral Infections in Immunocompromised Hosts

Meagan Deming, MD, PhD

Division of Clinical Care and Research

Institute of Human Virology, Baltimore MD.



**INSTITUTE OF
HUMAN VIROLOGY**



Background

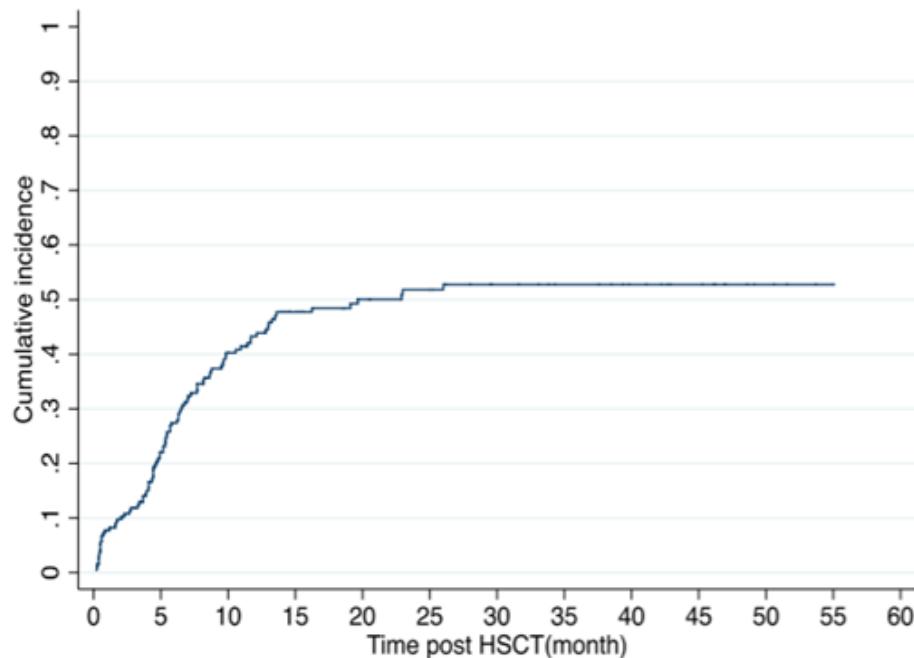
■ Viral Factors

- RNA viruses
 - Diversity & virologic escape
- Improved diagnostics

■ Host factors

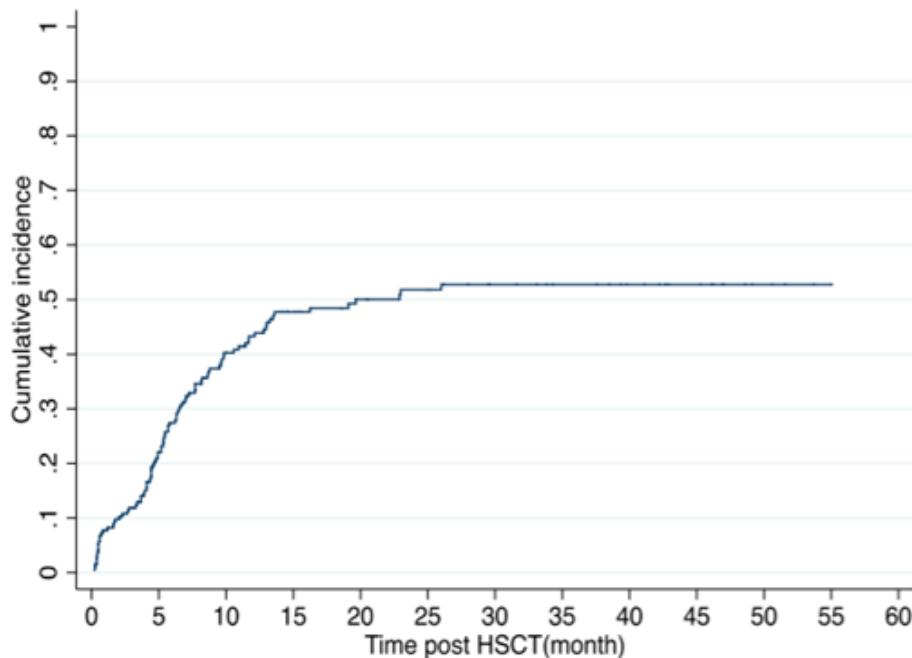
- Hematologic malignancies, chemotherapeutics
 - Tacrolimus, mycophenolate, steroids
- Hematopoietic stem cell transplants, solid organ transplants (particularly lung)
 - Lymphocyte-depleting antibodies (eg. thymoglobulin and alemtuzumab)

Incidence in HSCT Recipients

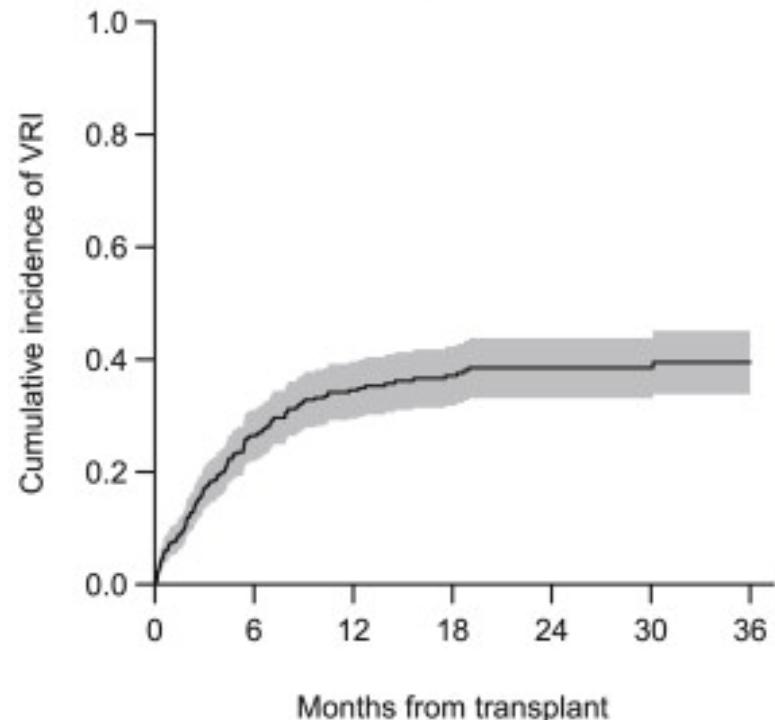


(Single center, Singapore, multiplex PCR)

Incidence in HSCT Recipients



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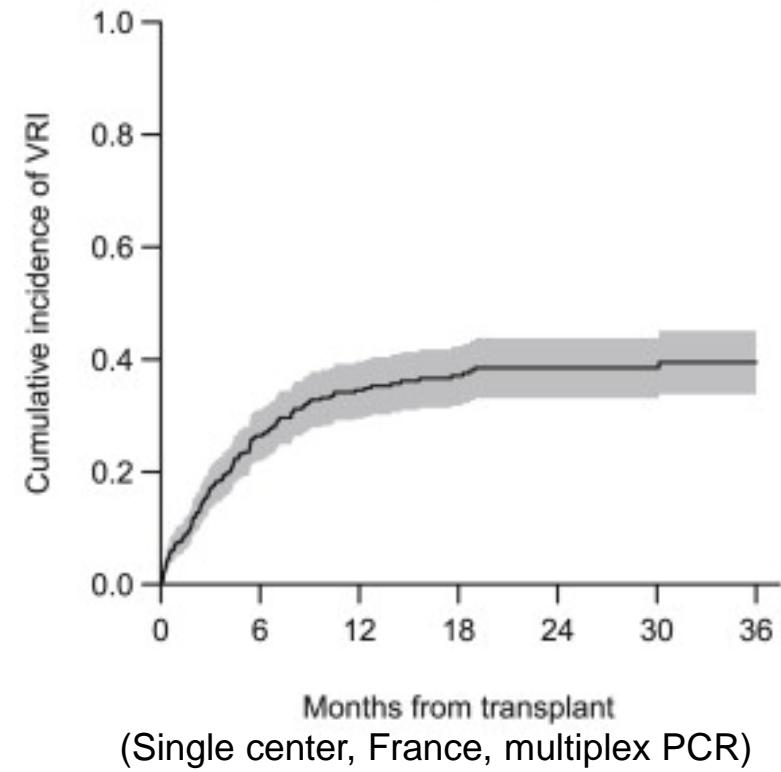
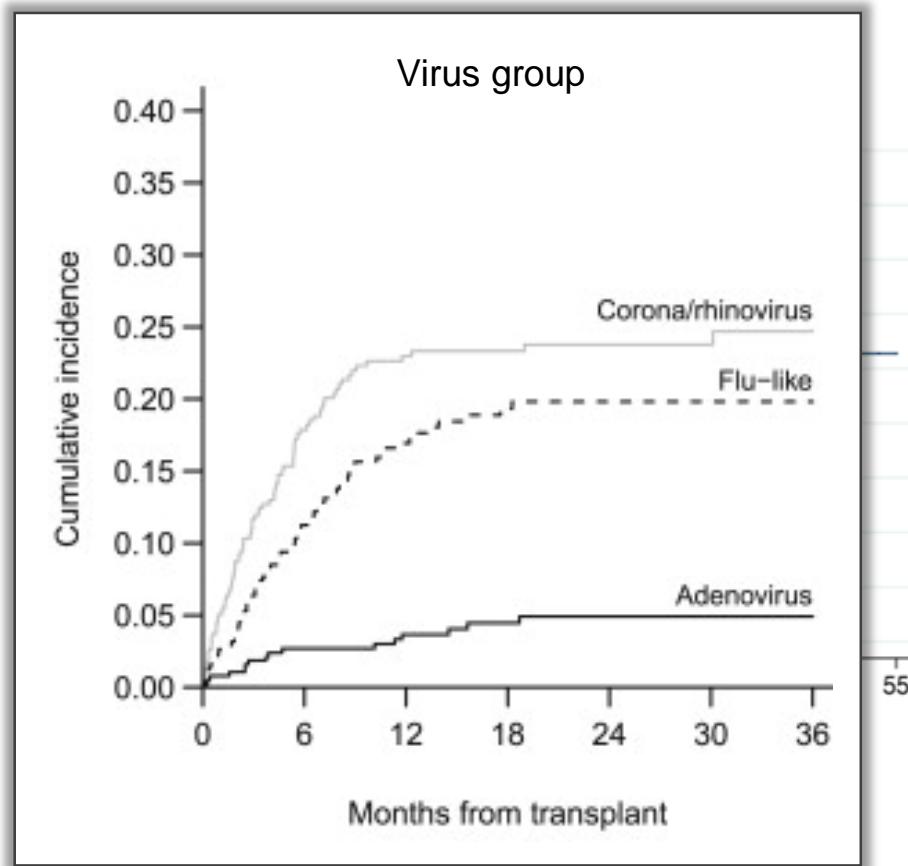


(Single center, France, multiplex PCR)

Cumulative incidence of respiratory viral infections in HCST patients approaches 40-50%.

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2. Wang L, et al. Transpl Infect Dis. 2017;19:1–9.

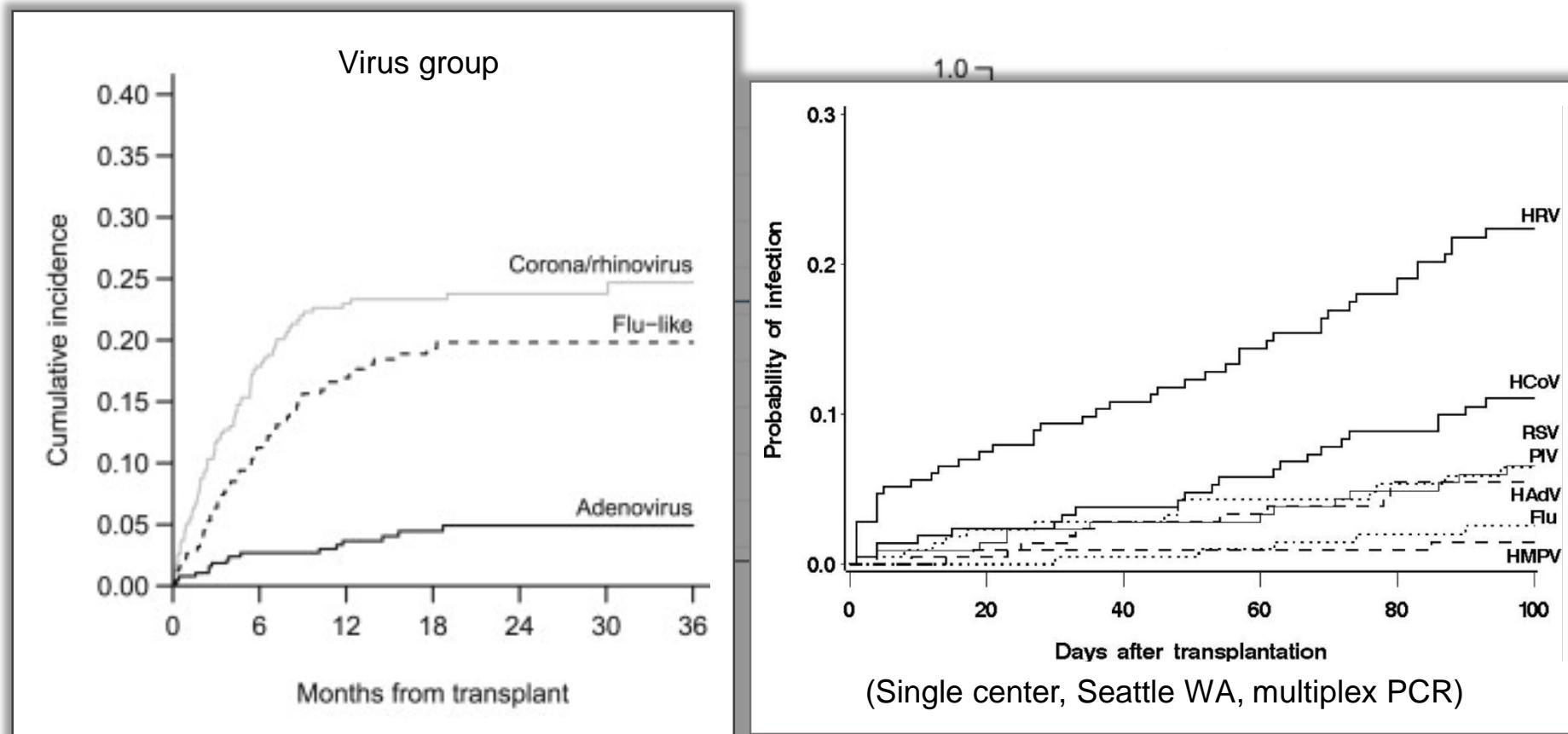
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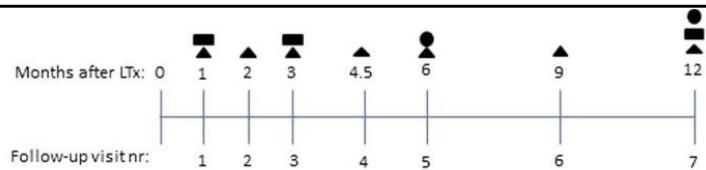
Diverse pathogens -
most common coronavirus and rhinovirus

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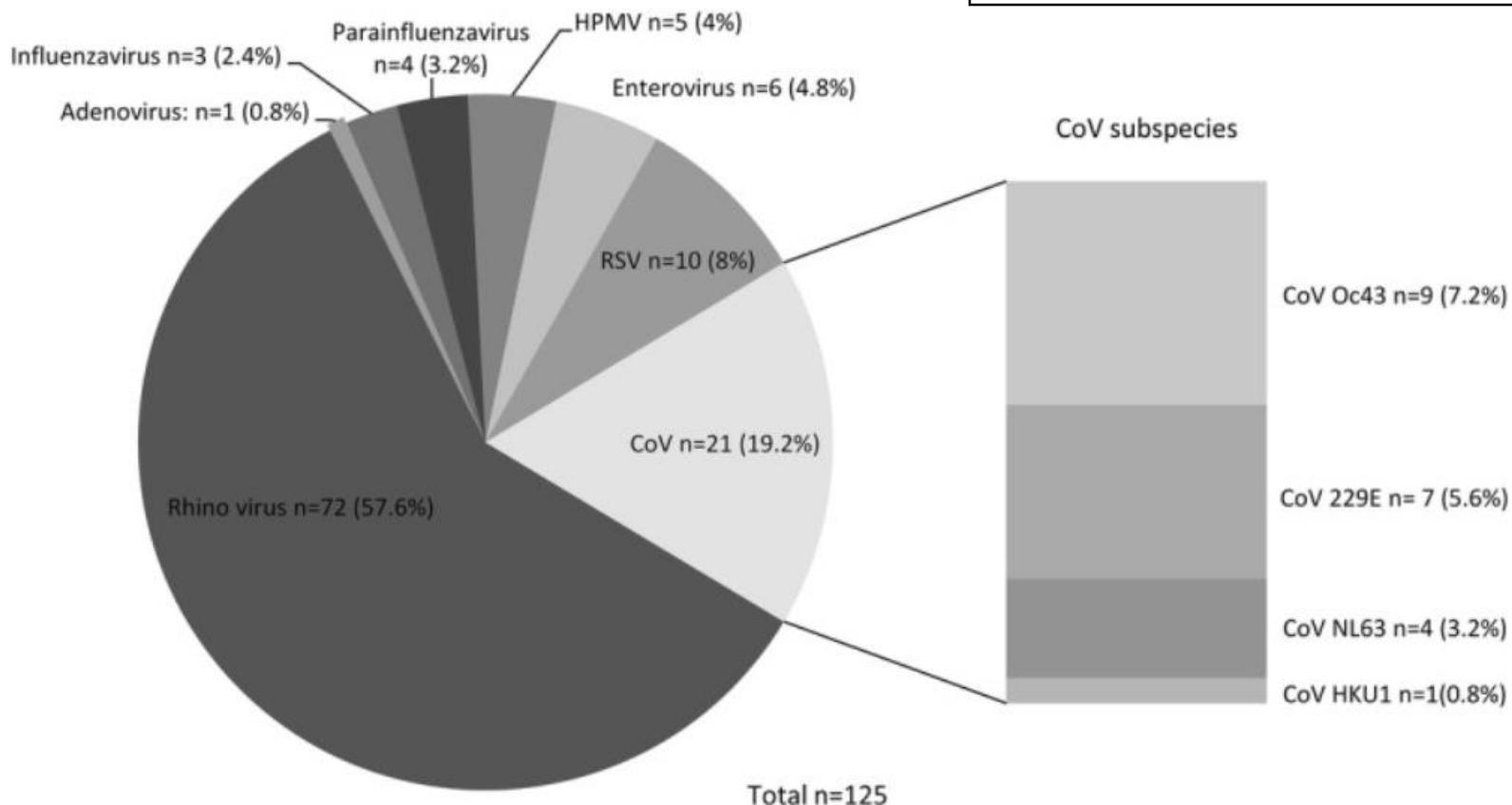
3. Milano F, et al. Blood. 2010;115(10):2088–94.

Lung Transplants

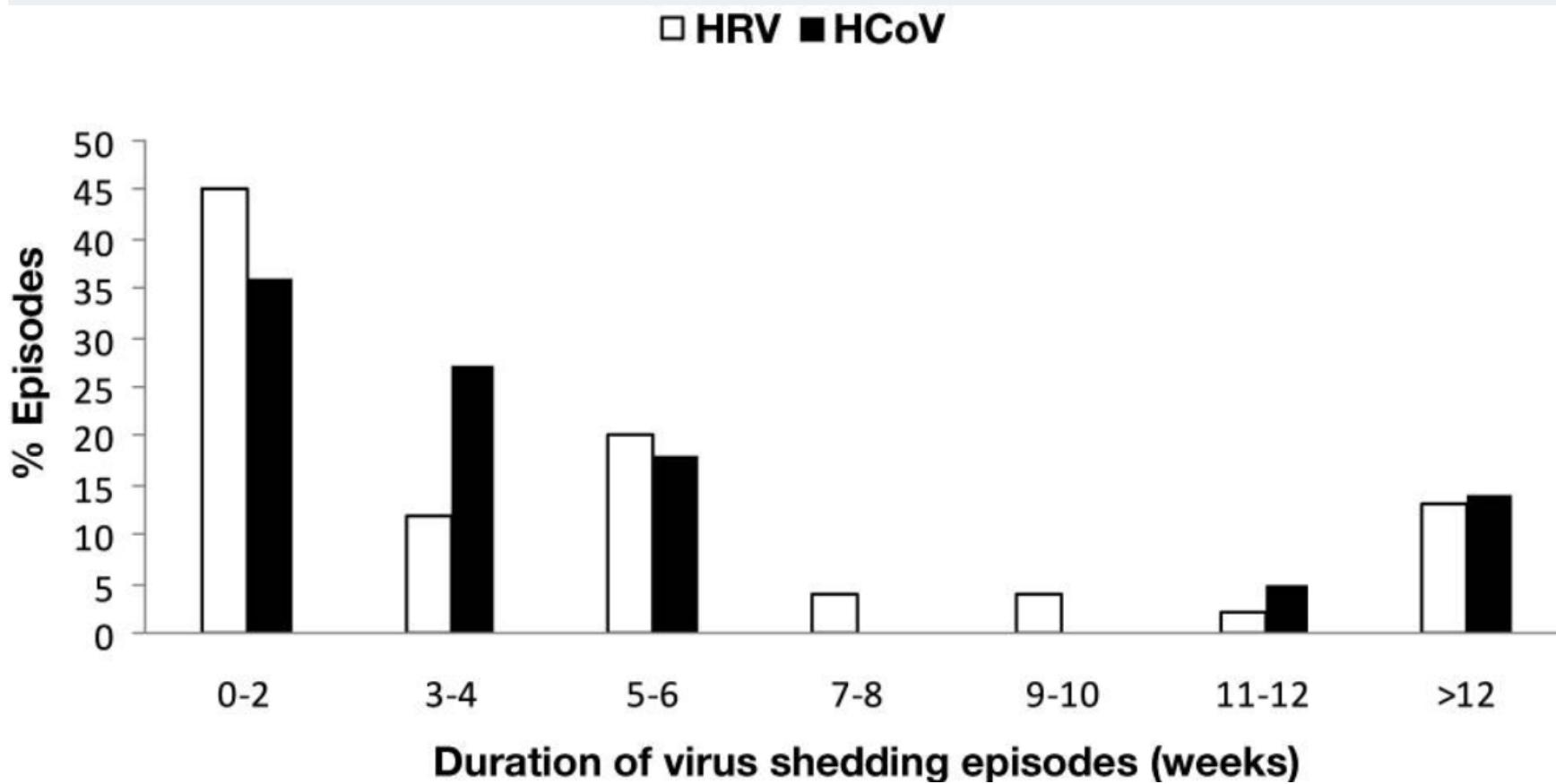
Of 98 patients, 51 (52%) developed viral RTI
Of 111 detected, 38 (34%) were lower RTI



Nasopharyngeal swabs for PCR

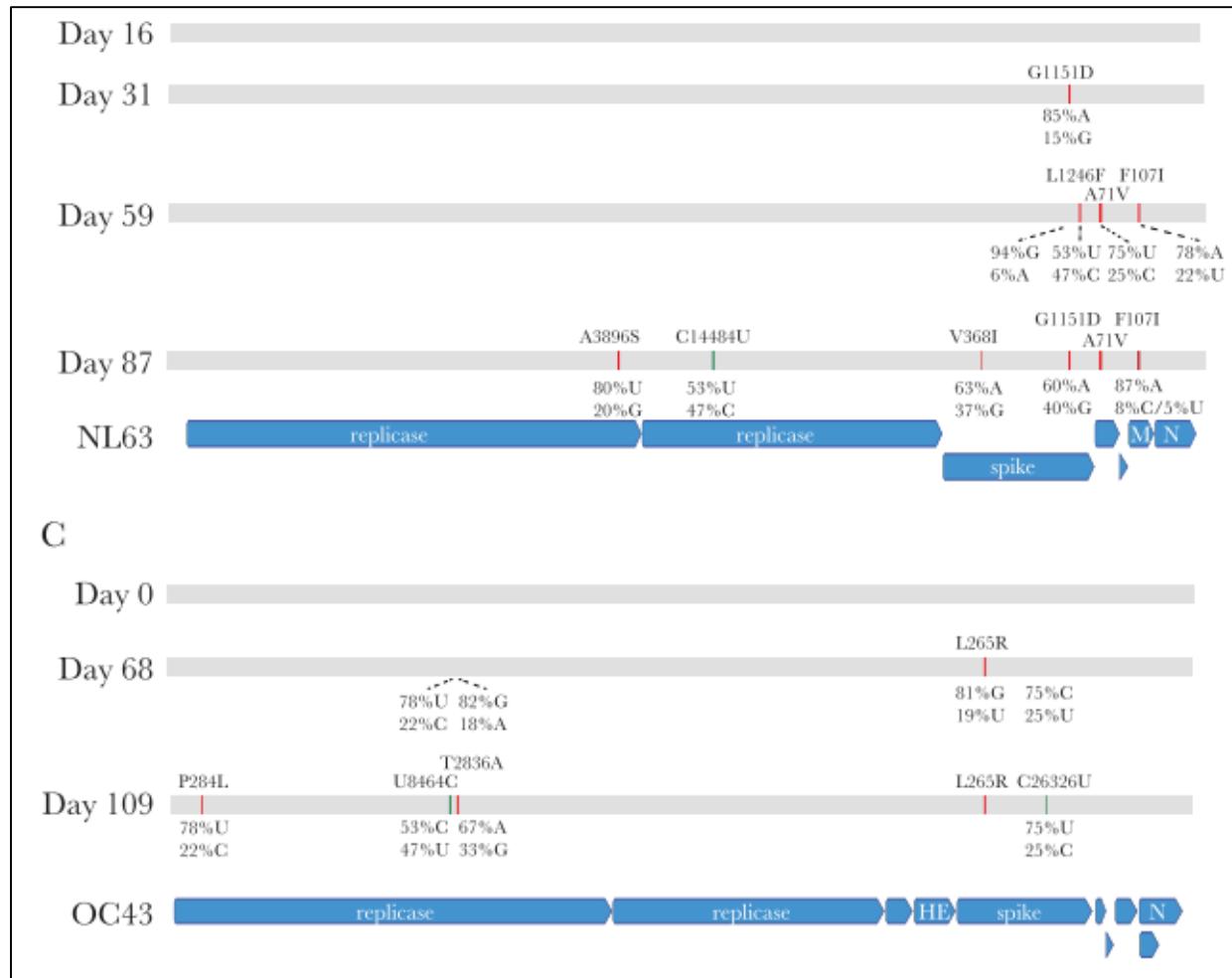


Viral Persistence



Viral Persistence

- No drastic intrahost evolution seen in 5 immunocompromised patients with persistent infection.



Viral Pneumonia

- Progress to lower respiratory tract infections in **33-58%** of patients with hematologic malignancies or HSCTs^{1,2}
 - Assoc. with severe lymphopenia (52%) vs. >200 cells/ μ L (31%)³

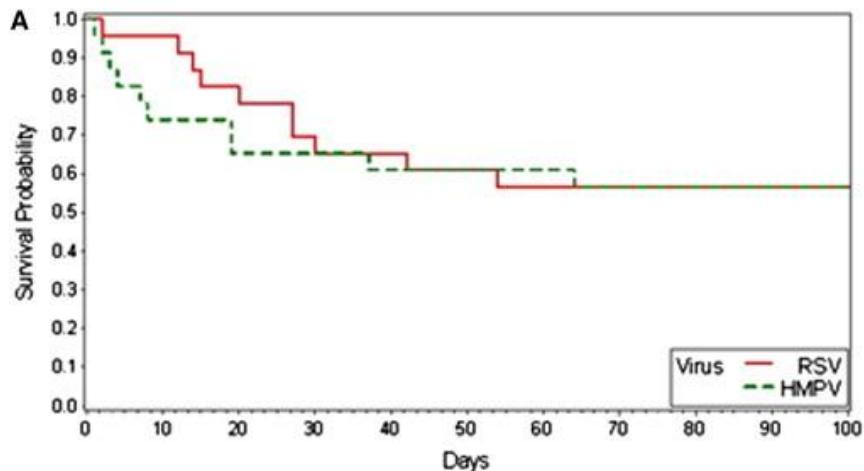
Progression to LRTI may be underestimated.

1. Vakil E, Evans SE. 2017;38(1):97–111.
2. Martino R, et al. Biol Blood Marrow Transpl. 2005;11(10):781–96.
3. Chemaly RF, et al. Medicine (Baltimore). 2006;85(5):278–87.
4. Renaud C, et al. Biol Blood Marrow Transplant. 2013;19(8):1220–6.

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- Mortality estimates^{1,4*}



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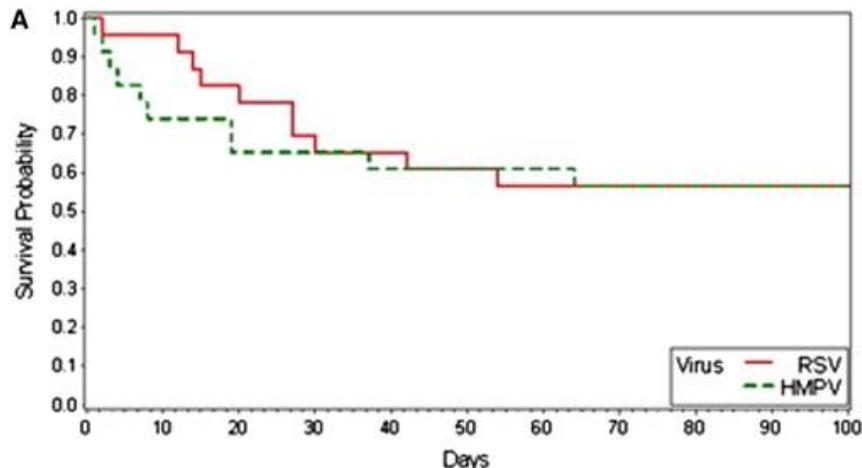
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- Mortality estimates^{1,4*}

- Influenza – 6 to 25%
- RSV – 29 to 88%
- hMPV – 0 to 43%⁶
- PIV – 17 to 35%
- Rhinovirus – 38-83%
- CoV – 0 to 11%⁵



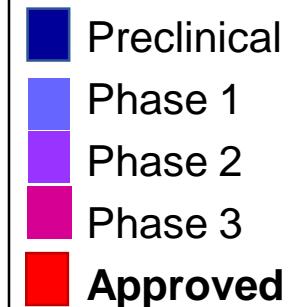
Retrospective cohort analysis of HSCT patients with confirmed RSV or HMPV LRTI – 43% mortality

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4. Renaud C, et al. Biol Blood Marrow Transplant. 2013;19(8):1220–6.
5. Eichenberger EM, et al. Bone Marrow Transplant. 2018
6. Shah DP, et al. Cancer Lett. 2016;379(1):100–6.

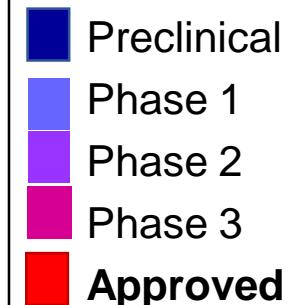
Therapeutic Targets

- IVIG, Flu-IVIG – (off label) RSV, influenza



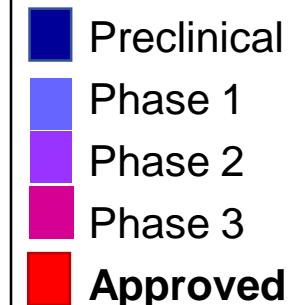
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 - PUL-042 (TLR9 & TLR2/6) – **broad spectrum**



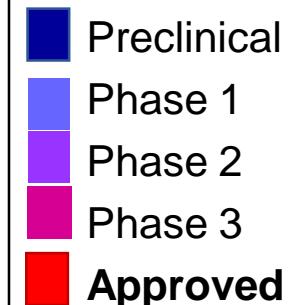
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- Receptor binding
 - HA monoclonals - Influenza
 - HN inhibitors - BCX 2798 & BCX 2855 - PIV)



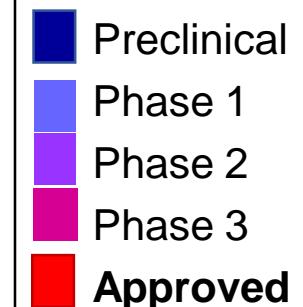
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- Fusion:
 - DAS181 – PIV, hMPV
 - Presatovir/GS-5806 – RSV
 - AK0529 – RSV



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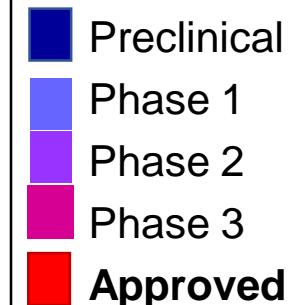
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- Fusion:
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- Release:
 - Neuraminidase (Oseltamivir, Peramivir, Zanamivir) – Influenza
 - M2 (amantadine) – Influenza A



Therapeutic Targets

■ Nucleoside analog:

- Ribavirin – (off label: RSV, MPV, PIV)
- Favipiravir/T-705 – RNA viruses, **Influenza**
- Lumicitabine/ALS-8176 – **RSV, PIV, hMPV**
- Remdesivir/GS-5734 - **CoV**



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■ mRNA replication

siRNA

- Asvasiran/ALN-RSV01 – **RSV**

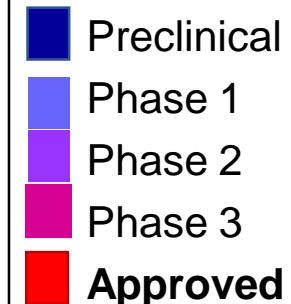
Cap-dependent endonuclease inhibitor

- Baloxavir – **Influenza**

Therapeutic Targets

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■ mRNA replication

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Cap-dependent endonuclease inhibitor

- Baloxavir – **Influenza**

■ Capsid inhibitors:

- Pleconaril – **RSV**
- BTA798/Vapendavir – **RSV**

Only influenza has approved therapeutics

Therapeutic Limitations

■ Neuraminidase inhibitors for hospitalized influenza

Early administration of neuraminidase inhibitors in adult patients hospitalized for influenza does not benefit survival

Characteristics	All patients (n = 506)	With early NAI therapy (n = 233)	Without early NAI therapy (n = 273)	p-value
Pneumonia	143 (28.3)	46 (19.7)	97 (35.5)	<0.001
ICU admission	38 (7.5)	10 (4.3)	28 (10.3)	0.01
Mechanical ventilation	22 (4.3)	6 (2.6)	16 (5.9)	0.07
Length of hospital stay, mean days (SD)	6.5 (7.6)	5.3 (4.5)	7.5 (2.9)	0.001
Influenza-related mortality	10 (2.0)	5 (2.1)	5 (1.8)	1.00

Early NAI associated with reduced risk of in-hospital mortality

Univariate Analysis

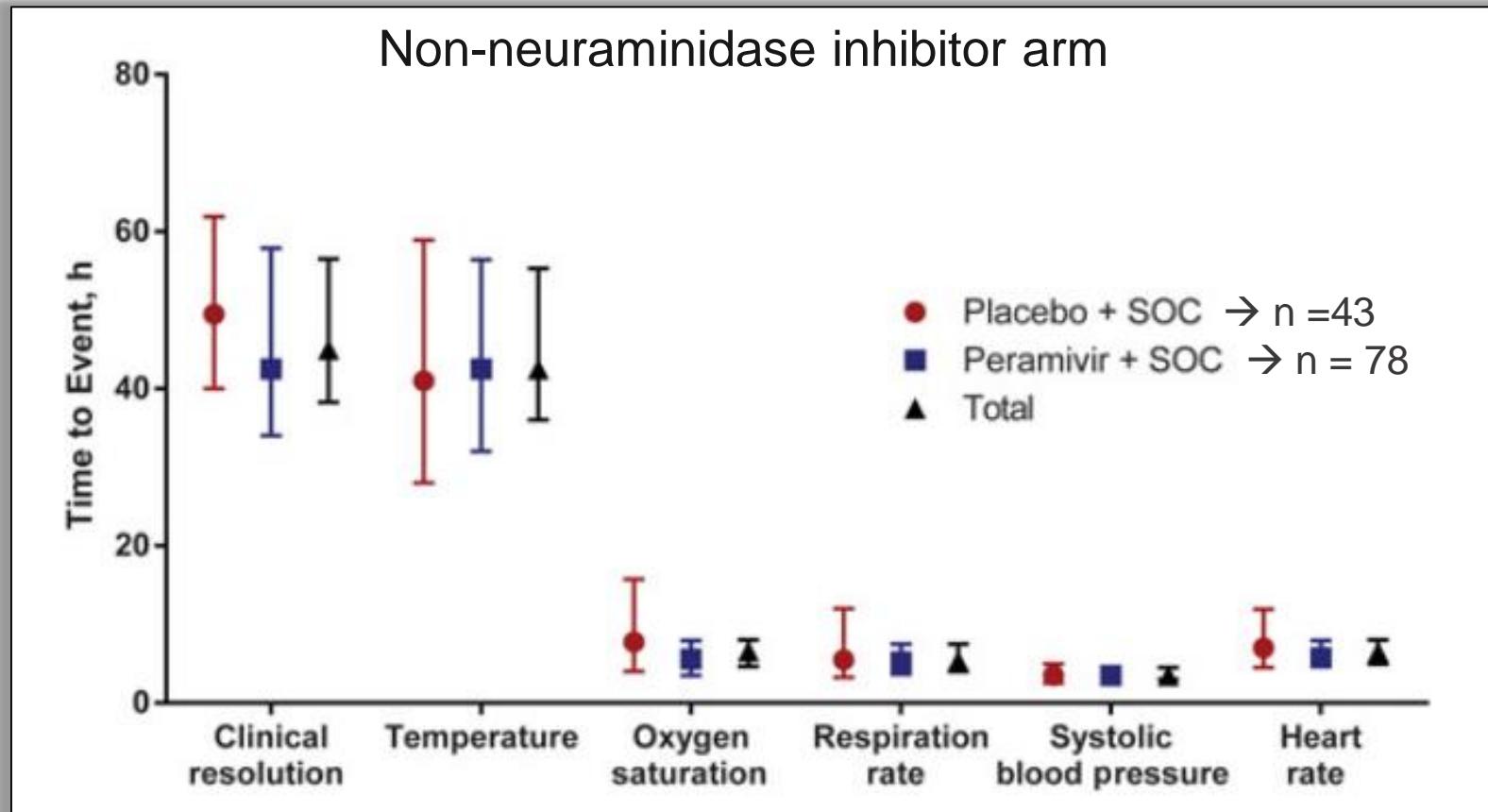
Multivariable Analysis

	OR (95% CI)	P value	OR (95% CI)	P value
Early NAI	0.16 (0.05-0.57)	0.004	0.20 (0.05-0.83)	0.026

Therapeutic Limitations

■ Neuraminidase inhibitors for influenza:

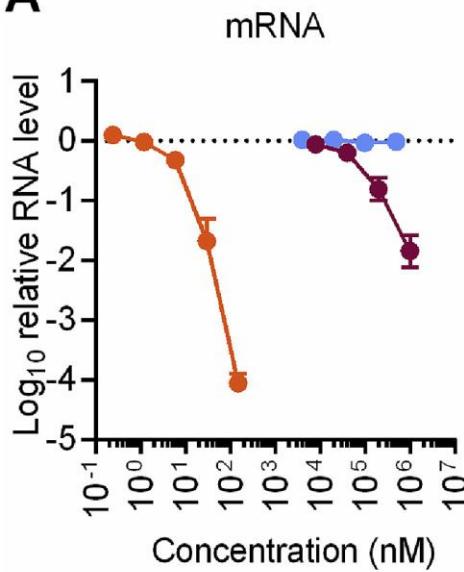
- Difficulty of placebo control in hospitalized



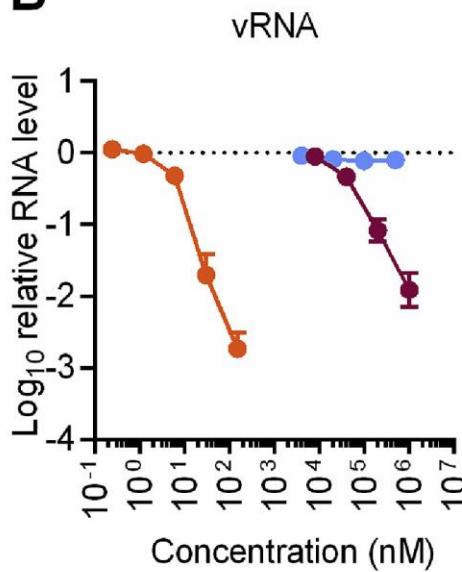
“Terminated due to futility... the increased usage of NAIs as SOC in the hospital setting created severe challenges to adequate patient enrollment in the non-NAI SOC group.”

Potent Antivirals In Development

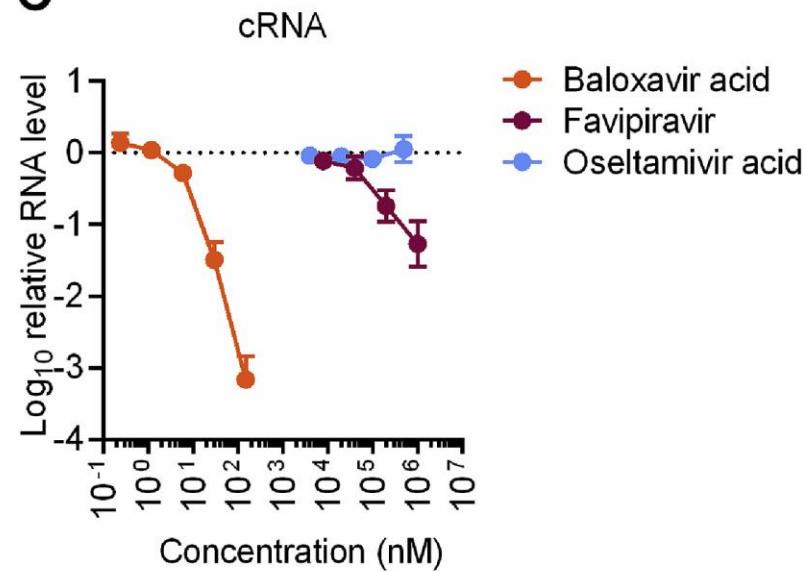
A



B



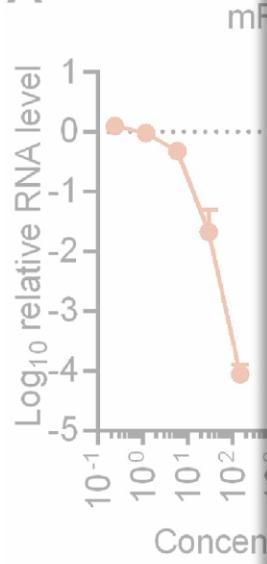
C



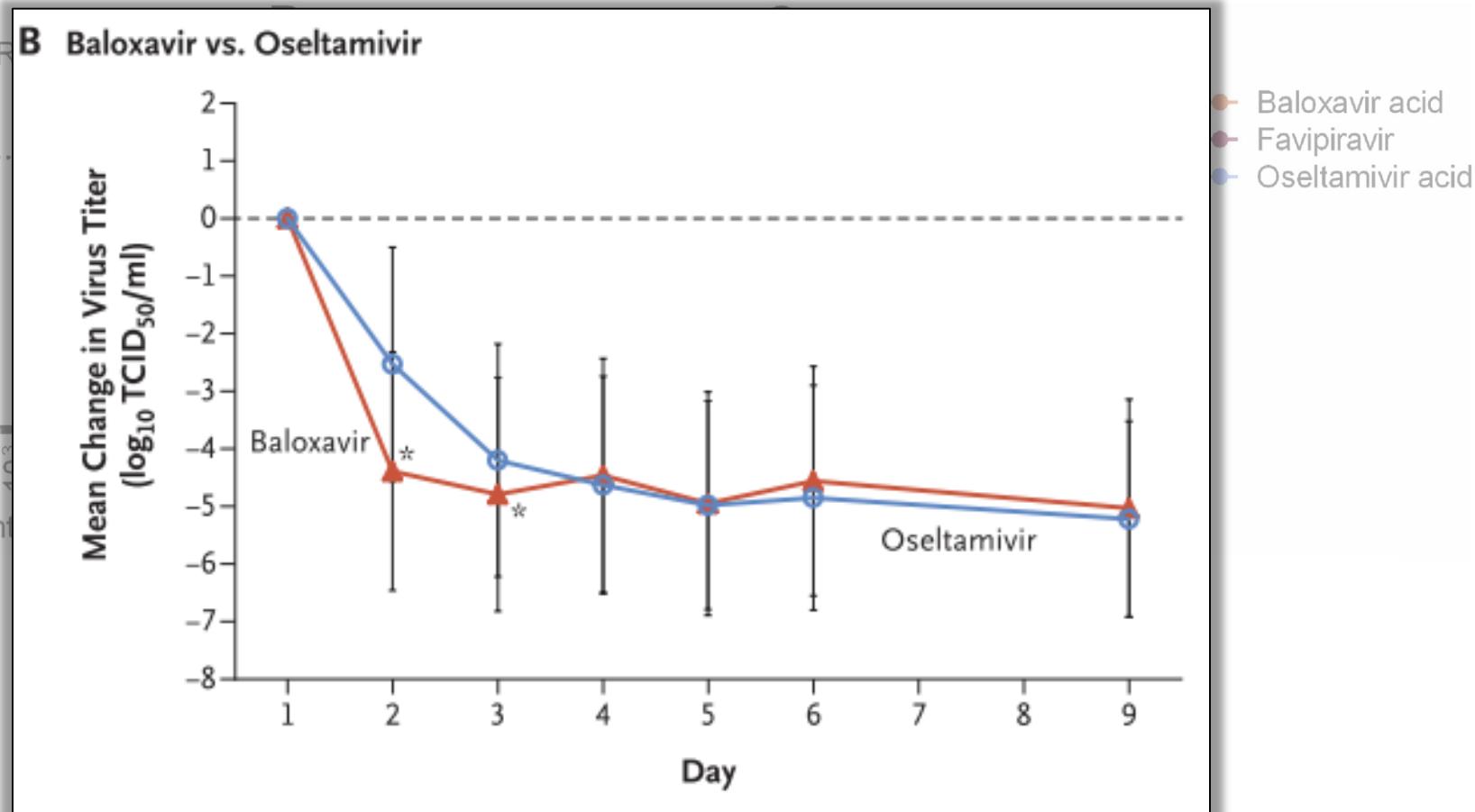
● Baloxavir acid
● Favipiravir
● Oseltamivir acid

Potent Antivirals In Development

A

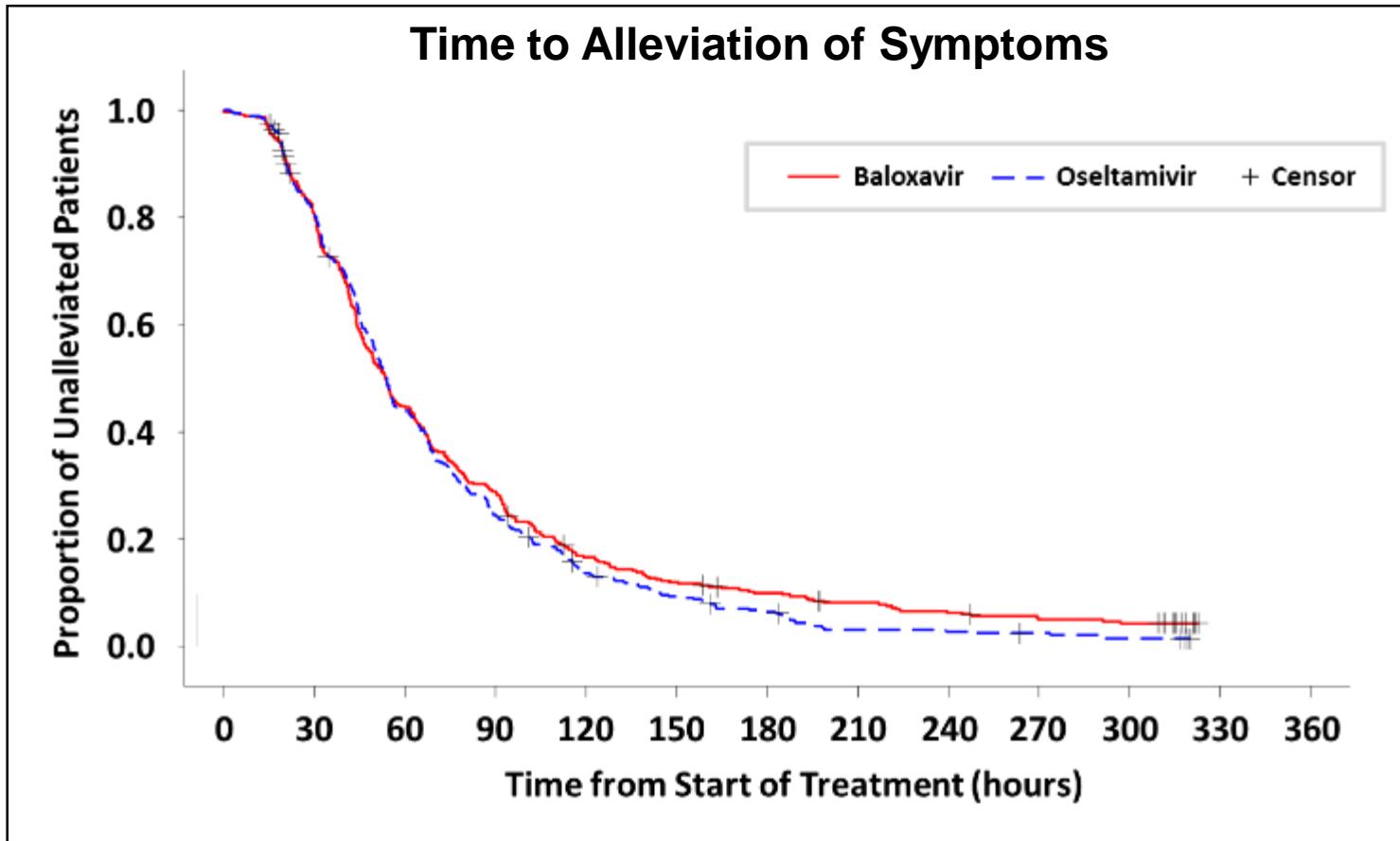


B Baloxavir vs. Oseltamivir



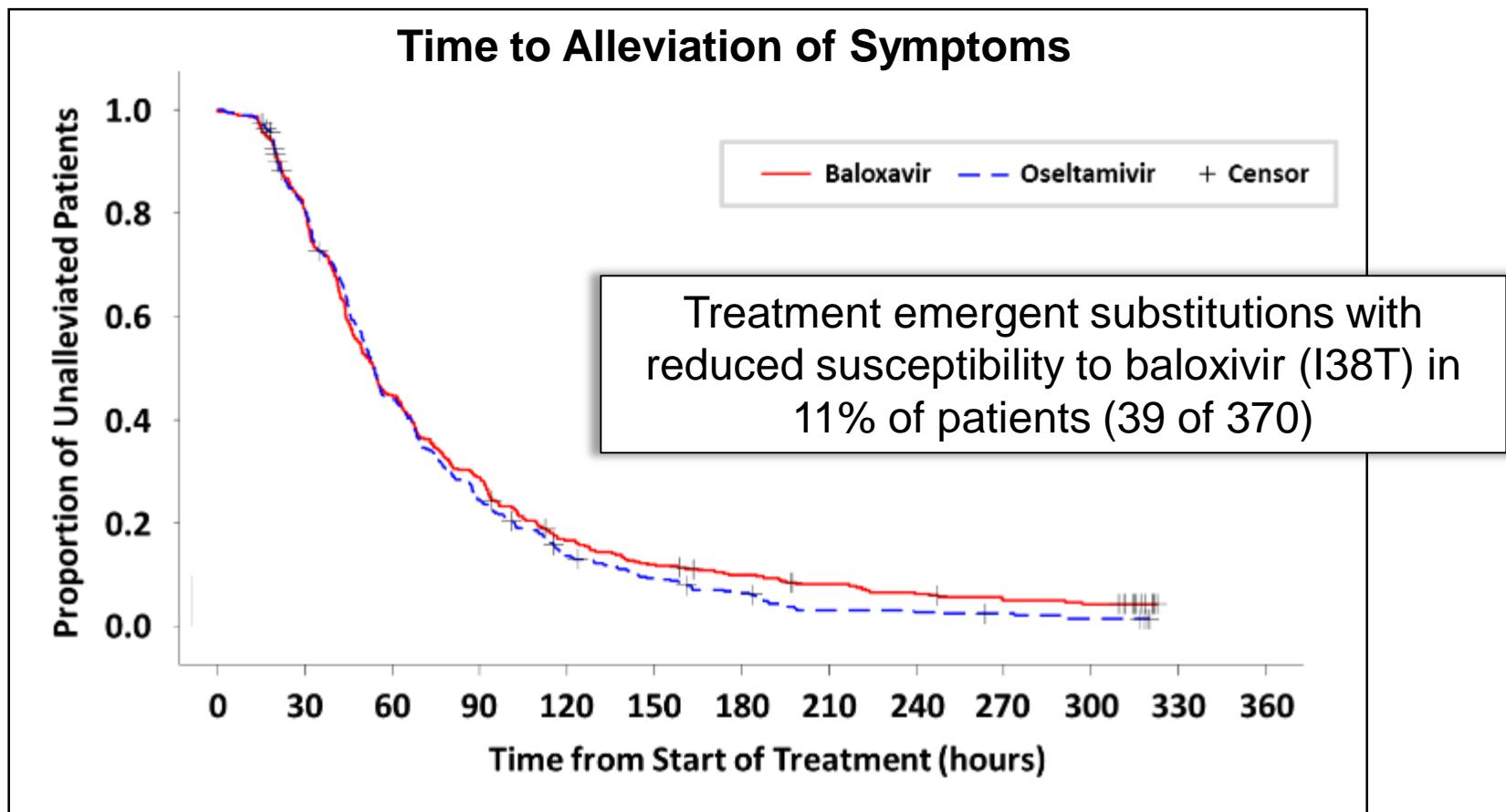
1. Noshi T, et al. Antiviral Res. 2018;160(Dec):109–17.
2. Hayden FG, et al. N Engl J Med. 2018;379(10):913–23

Limitations to Potent Antivirals?



- Limitation of rate of symptom resolution in healthy controls?
→ efficacy in immunocompromised hosts not yet assessed, nor in critically ill and hospitalized

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Summary

- Immunocompromised hosts have significant risk for complicated respiratory viral infections
 - Incidence of 40-50% in this population
 - Leukopenia associated with progression to lower respiratory tract infection in 30-50%, with associated morbidity/mortality
 - Diagnostics have improved, therapeutics lag behind
 - Ideal population for study
- Anticipated pitfalls
 - Limitation in therapeutic efficacy after infection established
 - Need for immunomodulatory therapeutics?
 - Selection of resistance
 - Need for combination therapies?

Acknowledgements

Institute of Human Virology

Shyamasundaran Kottilil

Eleanor Wilson

Bhawna Poonia



Center for Vaccine Development

Marcelo B. Sztein



University of Maryland Division of Infectious Disease

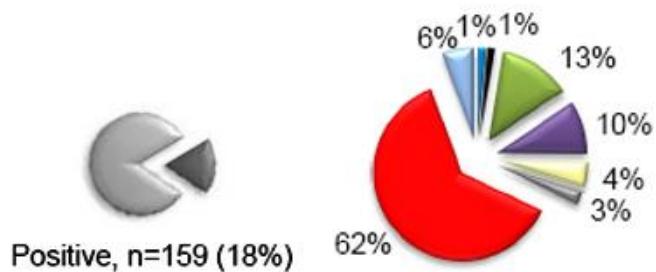
David Riedel



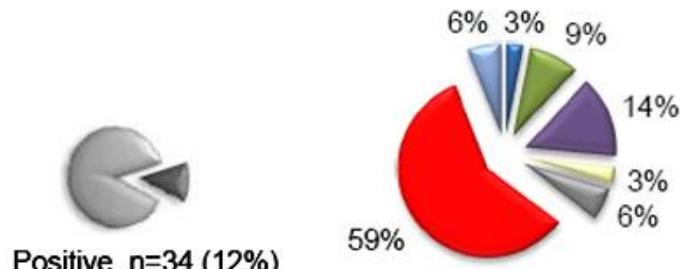
Lung Transplants

A

Nasopharyngeal specimens, n = 884

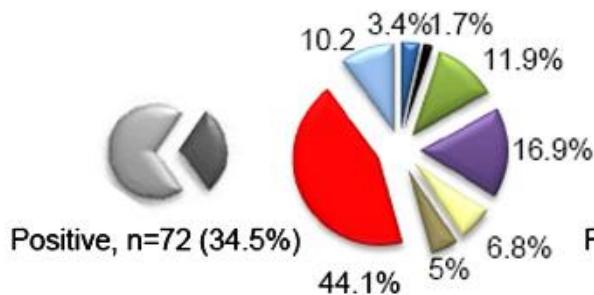


BAL specimens, n = 276

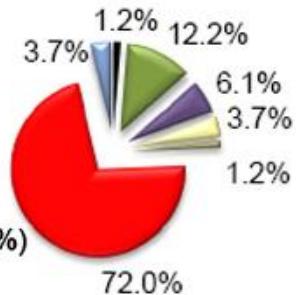


B

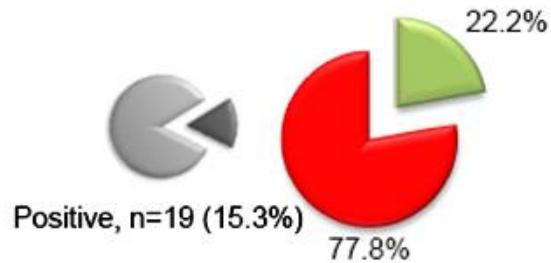
Emergency visits (n=209)



Pre-scheduled visits (n=570)



Regular visits (n=124)



Overall proportion of ■ positive or negative (RT)-PCR■

■ Adenovirus ■ Bocavirus ■ Coronavirus ■ Influenza ■ Metapneumovirus ■ Parainfluenza ■ Picornavirus ■ RSV