

National Institute of Allergy and Infectious Diseases

Antivirals for the Prevention and Treatment of Respiratory Viruses in the Immunocompromised

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Allergy and
Infectious Diseases

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Disclosures

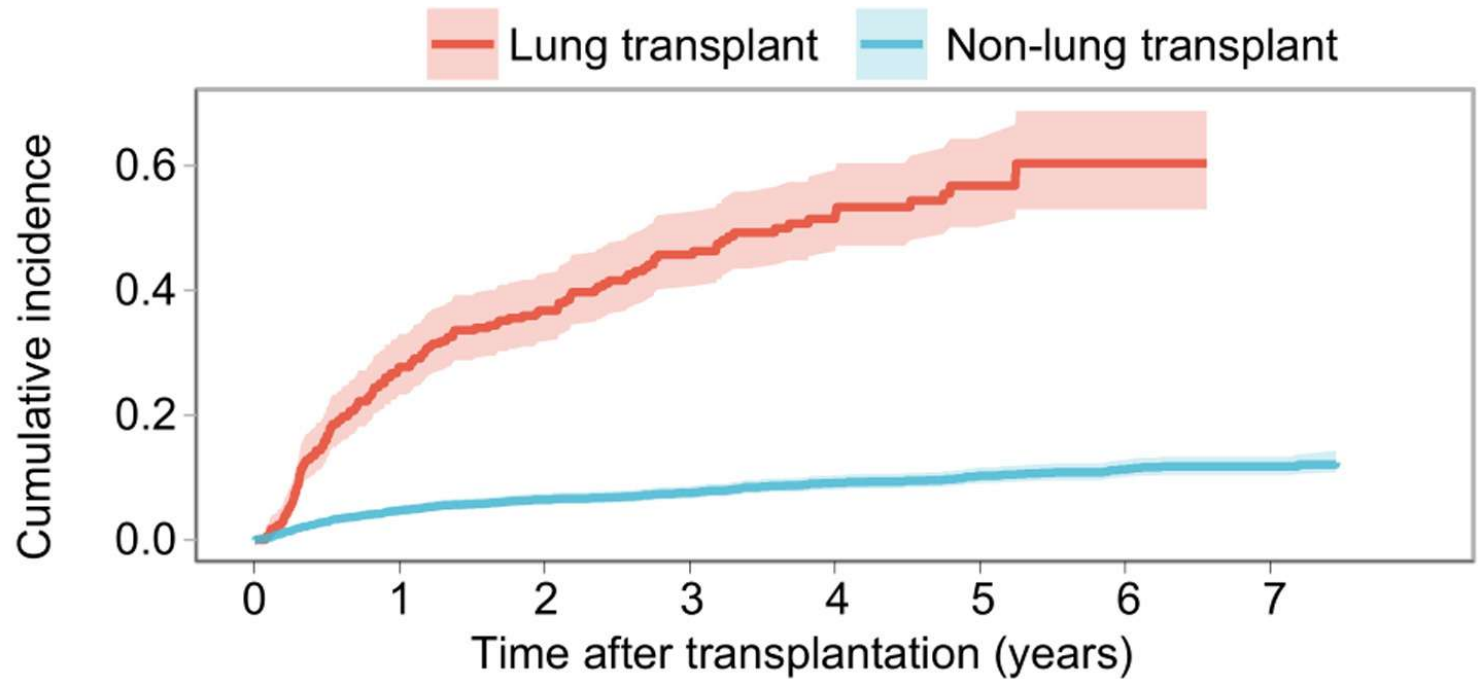
- Prior to joining NIH in December, I had research support from GSK, Roche and Genentech (paid to NU), had paid consultations from Adagio, ADMA Biologics, AlloVir, Cidara, Genentech/Roche, Janssen, Shionogi, Takeda, Viracor Eurofins and served on DSMBs for Allovir, CSL Behring, Janssen, Merck, Sequiris, Takeda, Talaris
- Ongoing royalties from UpToDate
- Editor-in-Chief of ***Transplant Infectious Disease***
- Will present unapproved therapies and non-FDA approved doses

Prevention & Treatment of RVI in ICH

- Epidemiology and Unique Features of RVI in ICH
- Influenza
- RSV
- SARS-CoV-2
- Other RVI

RVI in Solid Organ Transplant Recipients

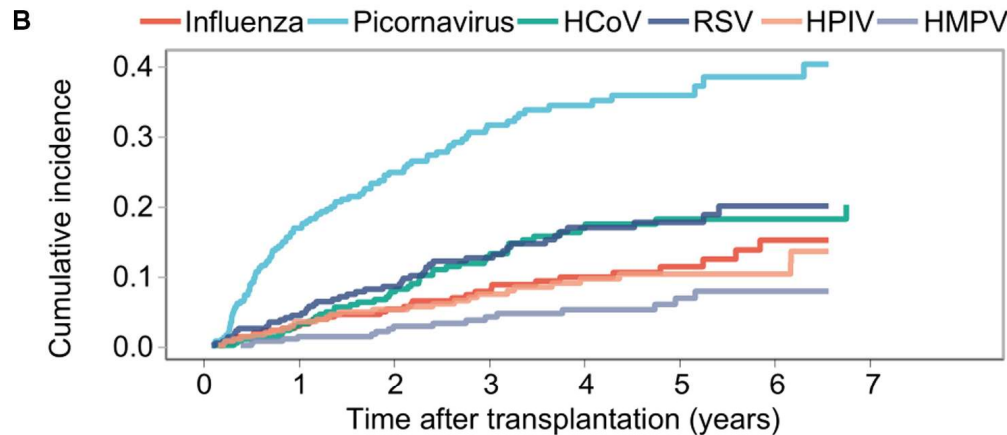
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Non-lung	2960	2387	1943	1558	1200	857	588	275	Number at risk
Lung	334	189	121	69	32	15	9	2	

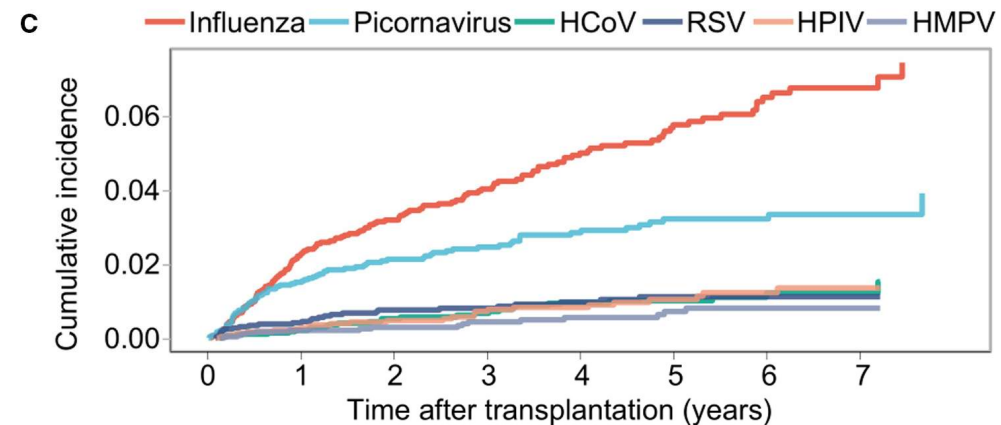
RVI in Solid Organ Transplant Recipients

Lung Transplant Recipients



Influenza	334	266	203	143	97	53	30	13	Number at risk
Picornavirus	334	222	153	96	57	30	19	8	
HCoV	334	266	199	137	89	52	32	15	
RSV	334	261	192	130	84	47	24	10	
HPIV	334	264	202	139	91	50	30	13	
HMPV	334	271	209	147	101	57	32	14	

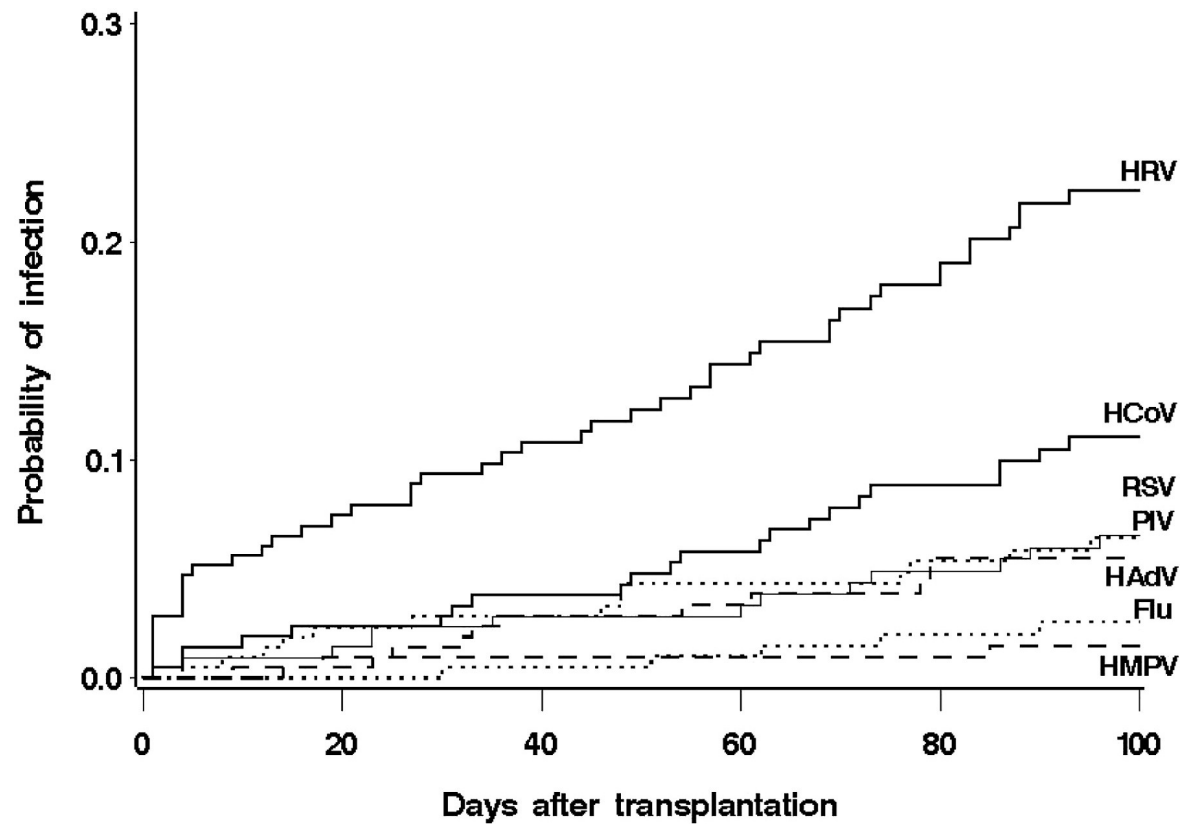
Non-Lung Transplant Recipients



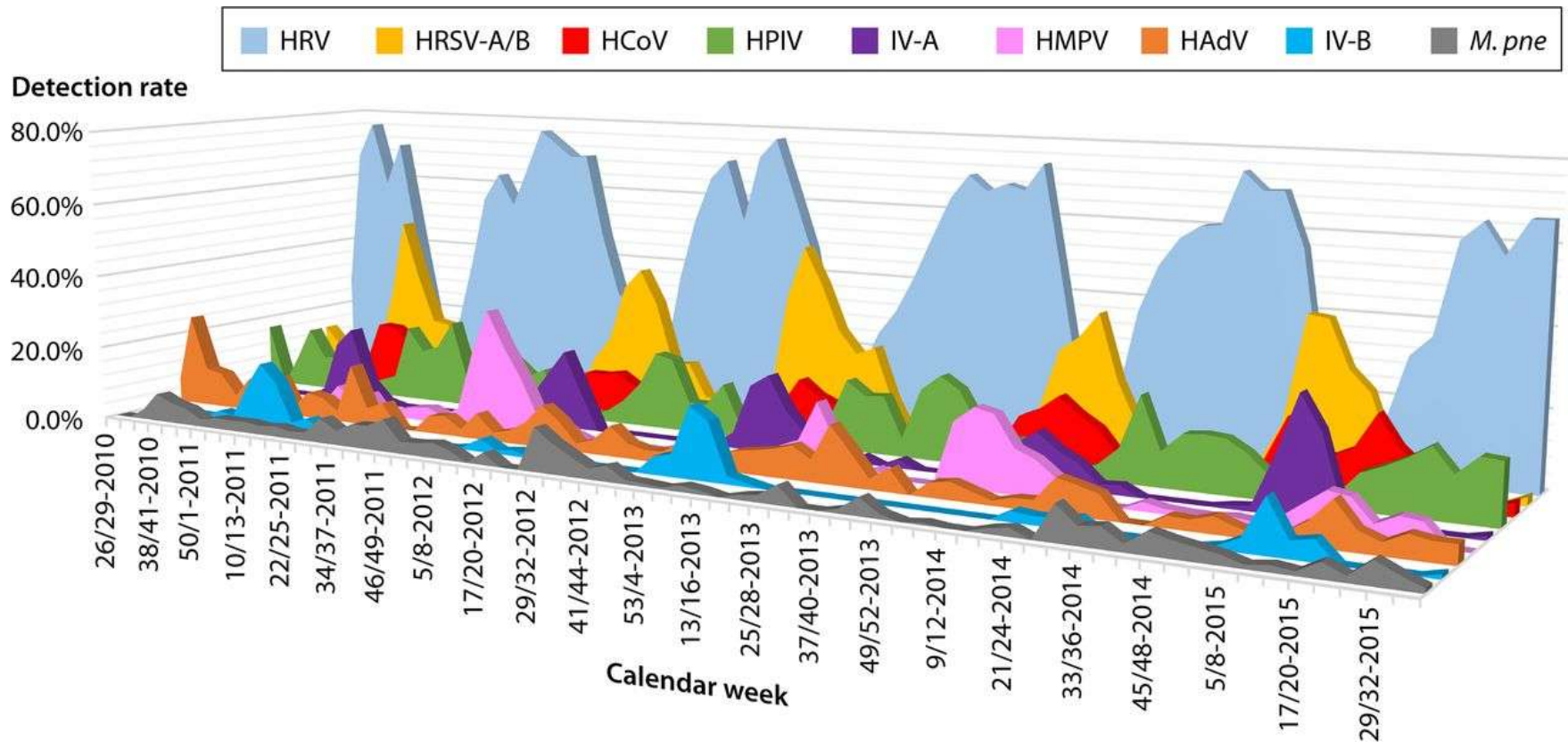
Influenza	2960	2452	2011	1605	1245	891	608	285	Number at risk
Picornavirus	2960	2467	2029	1633	1274	916	633	299	
HCoV	2960	2504	2062	1659	1298	940	644	305	
RSV	2960	2498	2057	1663	1300	939	646	306	
HPIV	2960	2502	2062	1659	1298	936	646	302	
HMPV	2960	2505	2069	1665	1300	939	647	306	

Epidemiology of RVIs: *HSCT*

Cumulative Incidence of RVI in 215 HSCT Recipients



Seasonality of RVI in Immunocompromised

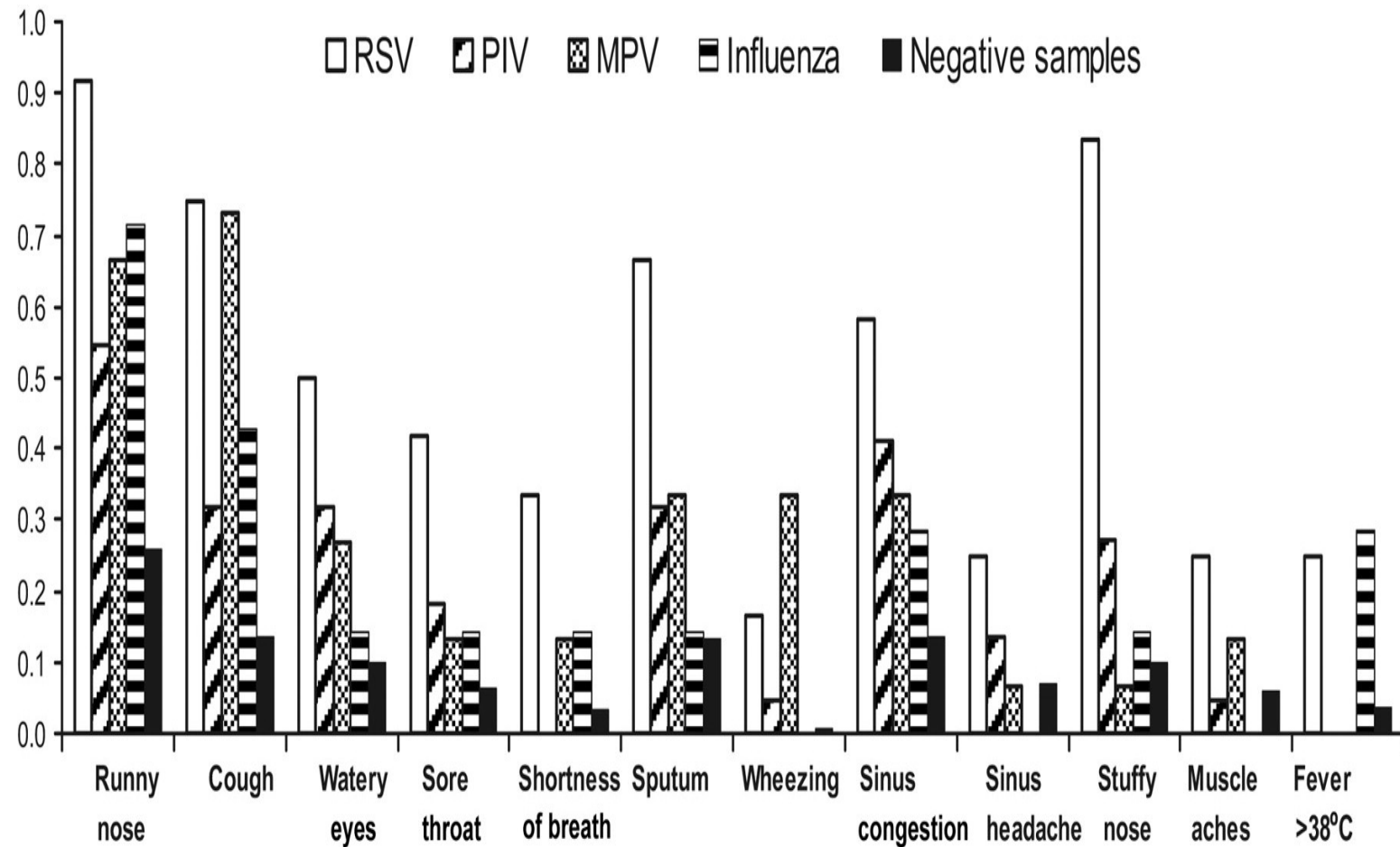


RVI in Lung Transplant: *Clinical Presentation*

Table 3 Symptomatology and hospitalisation rate associated with viral infection in lung transplant recipients (n=174)

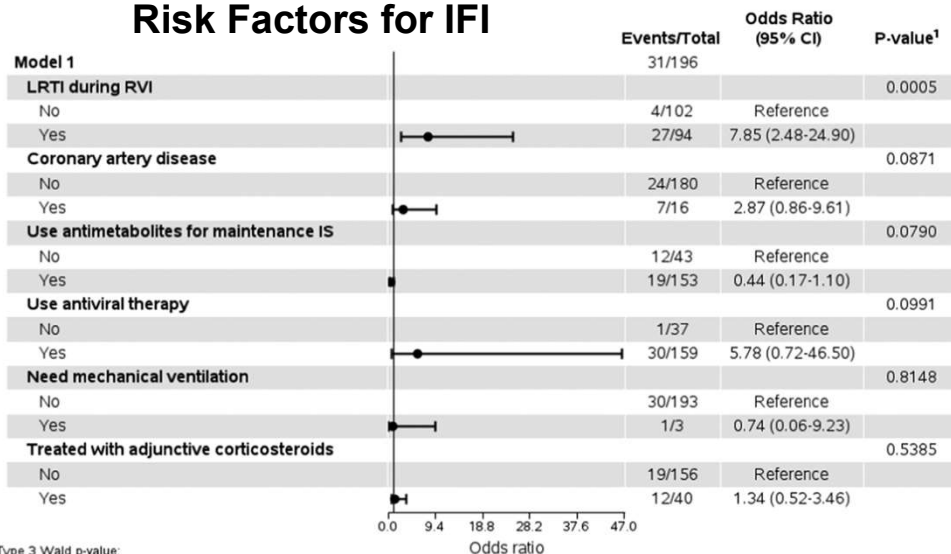
	Picornavirus (n=105)	Coronavirus (n=22)	Influenza (n=18)	RSV (n=11)	HMpV (n=8)	PIV (n=6)	Bocavirus (n=2)	Adenovirus (n=2)
New respiratory symptoms	67.6 (57.8 to 76.4)	72.7 (49.8 to 89.3)	88.8 (65.3 to 98.6)	90.9 (58.7 to 99.8)	75.0 (34.9 to 96.8)	100 (54.1 to 100)	50.0 (1.3 to 98.7)	100 (15.8 to 100)
Fever	14.3 (8.22 to 22.5)	13.6 (2.9 to 34.9)	61.1 (35.7 to 82.7)	9.1 (0.2 to 41.3)	12.5 (0.3 to 53.6)	0 (0 to 45.9)	0 (0 to 84.2)	50.0 (1.3 to 98.7)
Rhinorrhoea	42.8 (33.2 to 52.9)	50.0 (28.2 to 71.8)	66.7 (40.9 to 86.5)	81.8 (48.2 to 97.7)	75.0 (34.9 to 96.8)	33.3 (4.3 to 77.7)	50.0 (1.3 to 98.7)	0 (0 to 84.2)
Cough	41.9 (32.3 to 51.9)	36.4 (17.2 to 59.3)	61.1 (35.7 to 82.7)	72.7 (39.02 to 94.0)	50.0 (15.7 to 84.3)	100 (54.1 to 1)	50.0 (1.3 to 98.7)	100 (15.8 to 100)
Dyspnoea	36.2 (27.0 to 46.1)	31.8 (13.9 to 54.9)	44.4 (21.5 to 69.2)	36.4 (10.9 to 69.2)	25.0 (3.2 to 65.1)	83.3 (35.9 to 99.6)	50.0 (1.3 to 98.7)	100 (15.8 to 100)
Thoracic pain	6.6 (27.2 to 13.3)	18.2 (51.9 to 40.3)	22.2 (6.4 to 47.6)	9.1 (0.2 to 41.3)	0 (0 to 36.9)	16.7 (0.4 to 64.1)	0 (0 to 84.2)	100 (15.8 to 100)
Sputum	23.8 (16.0 to 33.1)	18.2 (51.9 to 40.3)	44.4 (21.5 to 69.2)	45.5 (16.7 to 76.6)	50.0 (15.7 to 84.3)	83.3 (35.9 to 99.6)	50.0 (1.3 to 98.7)	100 (15.8 to 100)
Myalgia	7.6 (3.3 to 14.4)	4.5 (0.1 to 22.8)	27.8 (9.7 to 53.5)	27.3 (6.0 to 61.0)	12.5 (0.3 to 52.7)	0 (0 to 45.9)	0 (0 to 84.2)	50.0 (1.3 to 98.7)
Fatigue	31.4 (22.7 to 41.2)	22.7 (7.8 to 45.4)	55.6 (30.8 to 78.5)	63.6 (30.8 to 89.1)	6.3 (24.5 to 91.5)	66.7 (22.3 to 95.7)	50.0 (1.3 to 98.7)	50.0 (1.3 to 98.7)
Sore throat	13.3 (7.5 to 21.4)	13.6 (2.9 to 34.9)	55.6 (30.8 to 78.5)	45.5 (16.7 to 76.6)	0 (0 to 36.9)	50.0 (11.8 to 88.2)	0 (0 to 84.2)	0 (0 to 84.2)
Sum of symptoms: mean (SD)	2.2 (2.3)	2.1 (2.0)	4.4 (3.0)	3.9 (2.4)	2.9 (2.5)	4.3 (1.6)	2.5 (3.5)	5.5 (2.1)
Hospitalisation	18.1 (11.3 to 26.8)	22.7 (7.8 to 45.3)	44.4 (21.5 to 69.2)	0 (0 to 28.5)	12.5 (0.1 to 52.7)	50 (11.8 to 88.2)	0 (0 to 84.2)	100 (15.8 to 100)

RVI in HSCT: *Clinical Presentation*

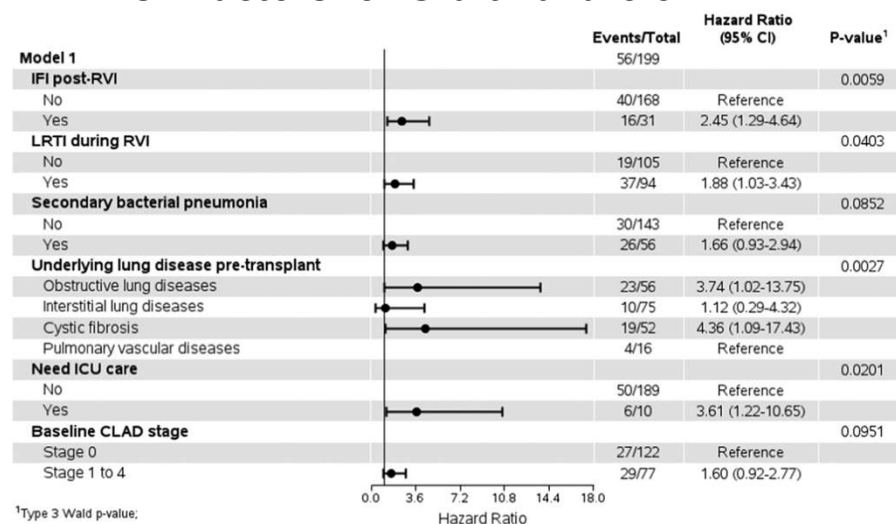


RVI in Lung Transplant: *Acute Complications*

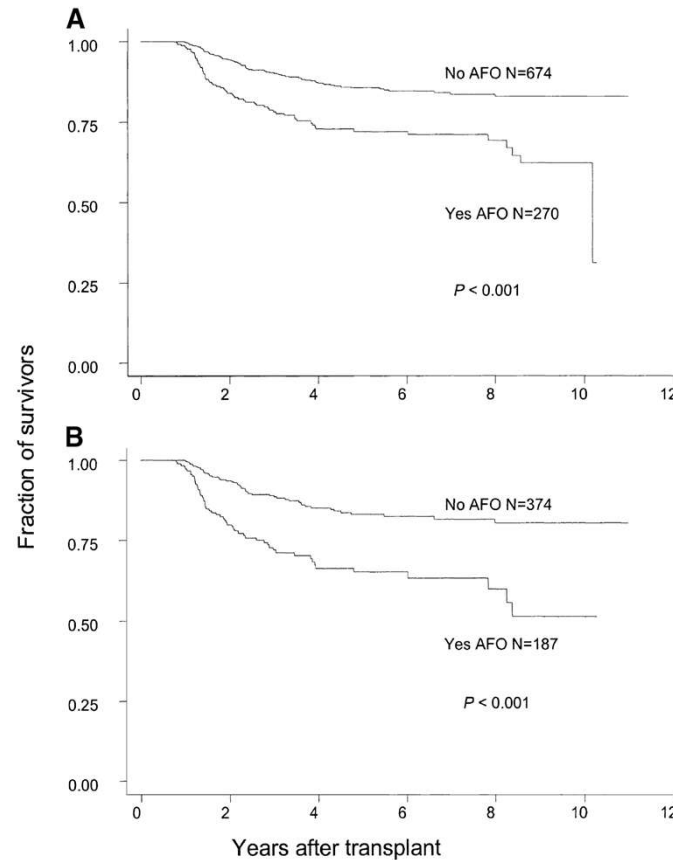
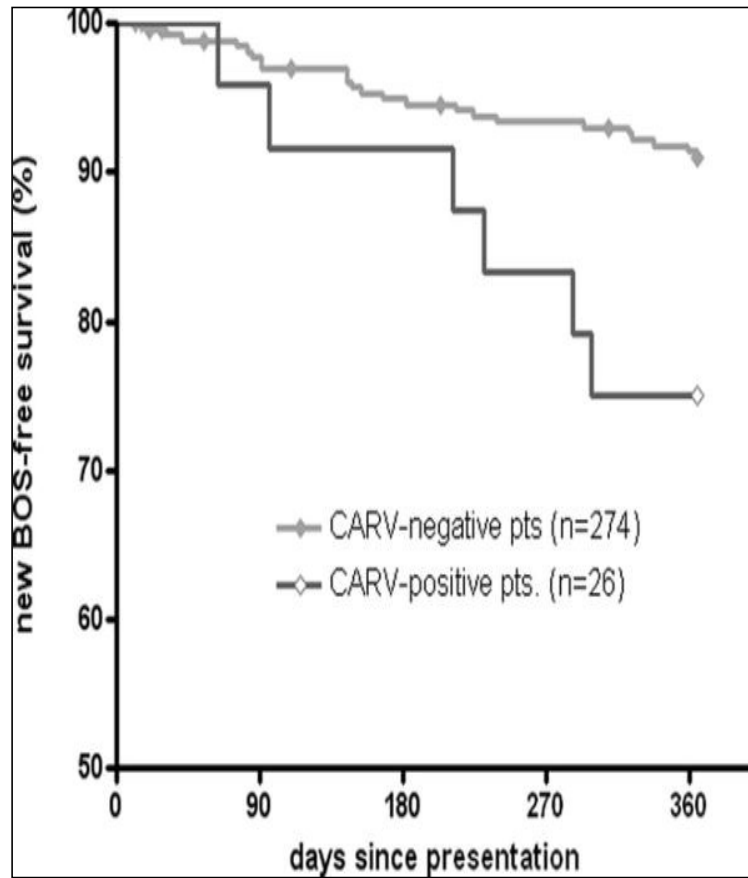
Risk Factors for IFI



Risk Factors for Graft Failure or CLAD



Epidemiology of RVI: *Long Term Complications*



- HR: 1.4
 - 95% CI 1.04 - 1.8
 - $P = 0.03$
- Greatest risk with PIV
 - HR ~18

Risk Stratification

TABLE 2 Clinical criteria proposed to identify patients undergoing allo-HCT at risk for complicated CARV lower RTID caused by HRSV, HPIV, or IV-A/B^a

University Hospital Basel immunodeficiency grading system		MD Anderson Cancer Center immunodeficiency scoring index	
Criterion or parameter	Score	Criterion or parameter	Score
Neutropenia, $<0.5 \times 10^9/\text{liter}$	1	Neutropenia, $<0.5 \times 10^9/\text{liter}$	3
Lymphopenia, $<0.1 \times 10^9/\text{liter}$	1	Lymphopenia, $<0.2 \times 10^9/\text{liter}$	3
Allo-HCT <6 months ago	1	Preengraftment or allo-HCT <1 months	1
GVHD of ≥ 2 or requiring treatment	1	GVHD (acute/chronic)	1
T-cell depletion <3 months prior to CARV Dx	1	Corticosteroids	1
B-cell depletion <3 months prior to CARV Dx	1	Myeloablative conditioning	1
Hypo- γ -globulinemia, <4.5 g/liter	1	Age, >40 yr	2
Maximal	7	Maximal	12
Moderate (MID)	0	Low risk	0–2
Severe (SID)	1	Moderate risk	3–6
Very severe (verySID)	2–7	High risk	7–12

^aAllo-HCT, allogeneic hematopoietic cell transplantation; CARV, community-acquired respiratory virus; Dx, diagnosis; GVHD, graft-versus-host disease; HRSV, human respiratory syncytial virus; HPIV, human parainfluenzavirus; IV-A/B, influenza virus A or B; RTID, respiratory tract infectious disease.

Prevention of Influenza: *Antiviral Prophylaxis*

RT-PCR

Protective efficacy = 74.9%

95% CI for difference: 2.3%, 10.7%

8.4% (20/238)



1.7% (4/237)



3.8% (9/238)



Culture

Protective efficacy = 88.8%

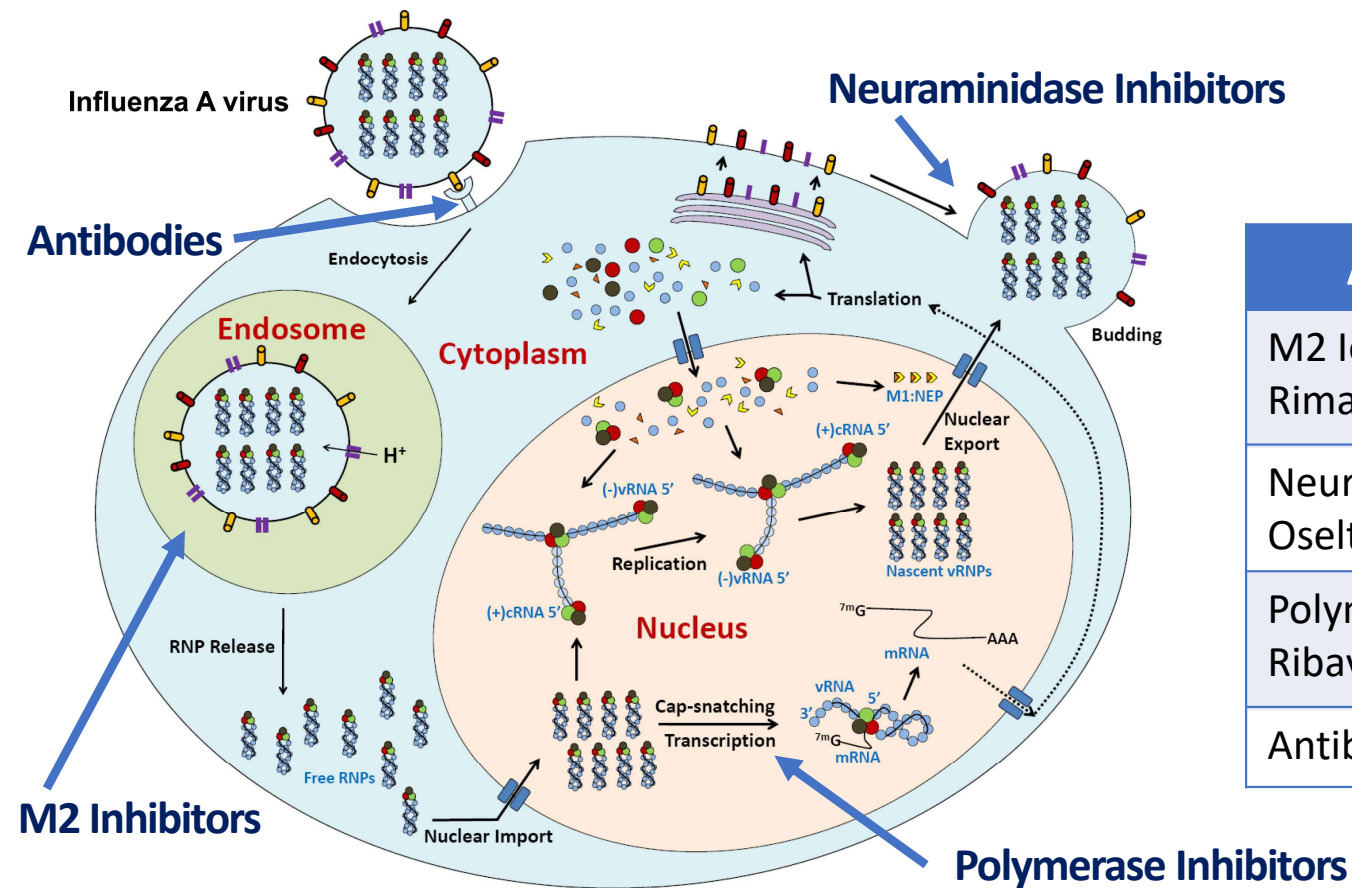
95% CI for difference: 0.7%, 6.6%

0.4% (1/237)



No change in IC_{50} with breakthrough viruses

Management of Influenza: *Antiviral Therapy*



Available Influenza Antivirals

M2 Ion Channel Inhibitors: Amantadine, Rimantadine

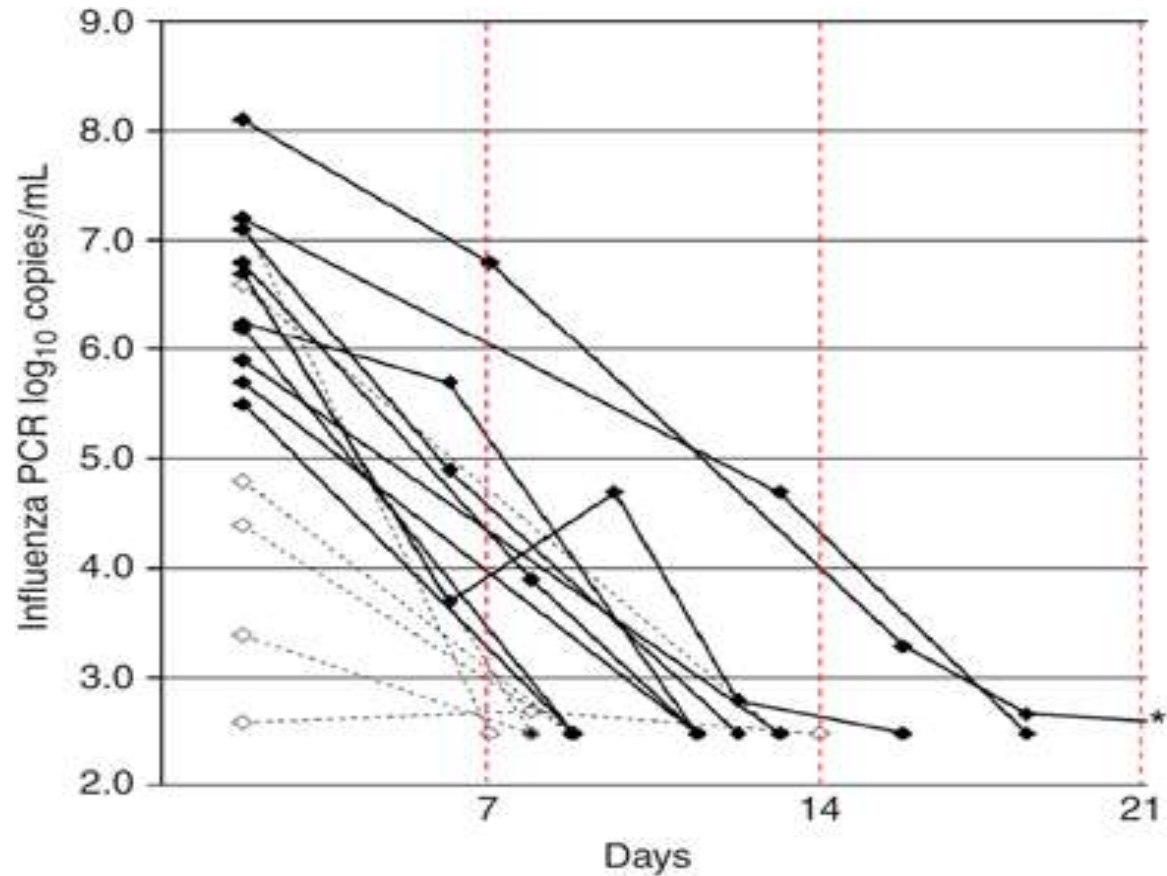
Neuraminidase Inhibitors: Laninamivir, Oseltamivir, Peramivir, Zanamivir

Polymerase Inhibitors: Baloxavir, Favipirivir, Ribavirin

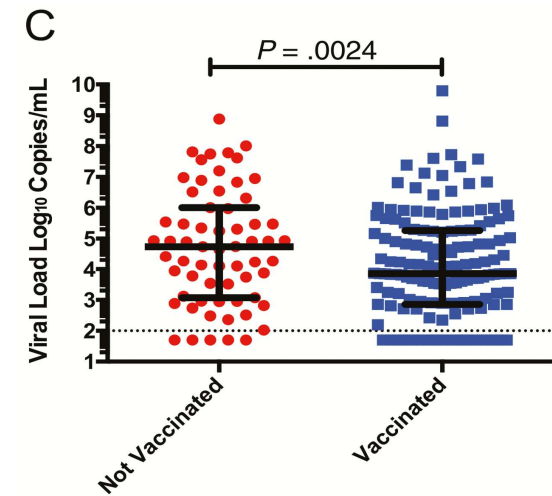
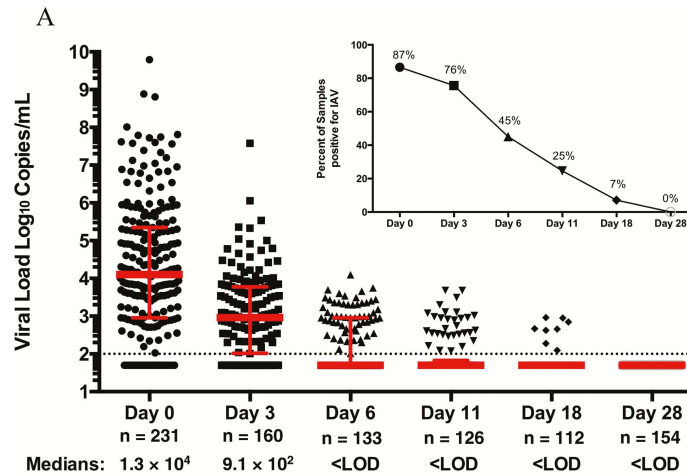
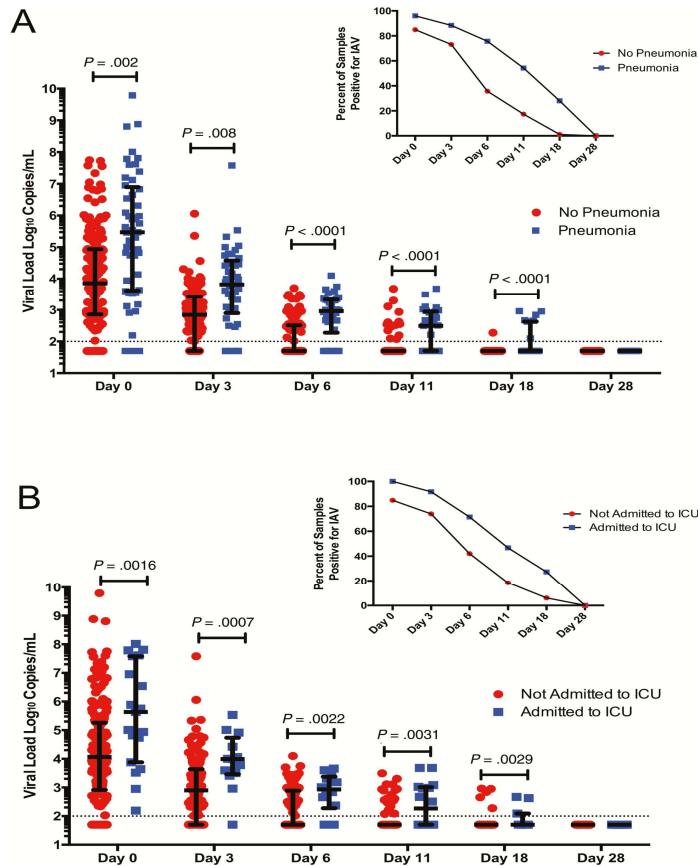
Antibodies: Monoclonal Ab, IgIV, Plasma

Treatment of Influenza

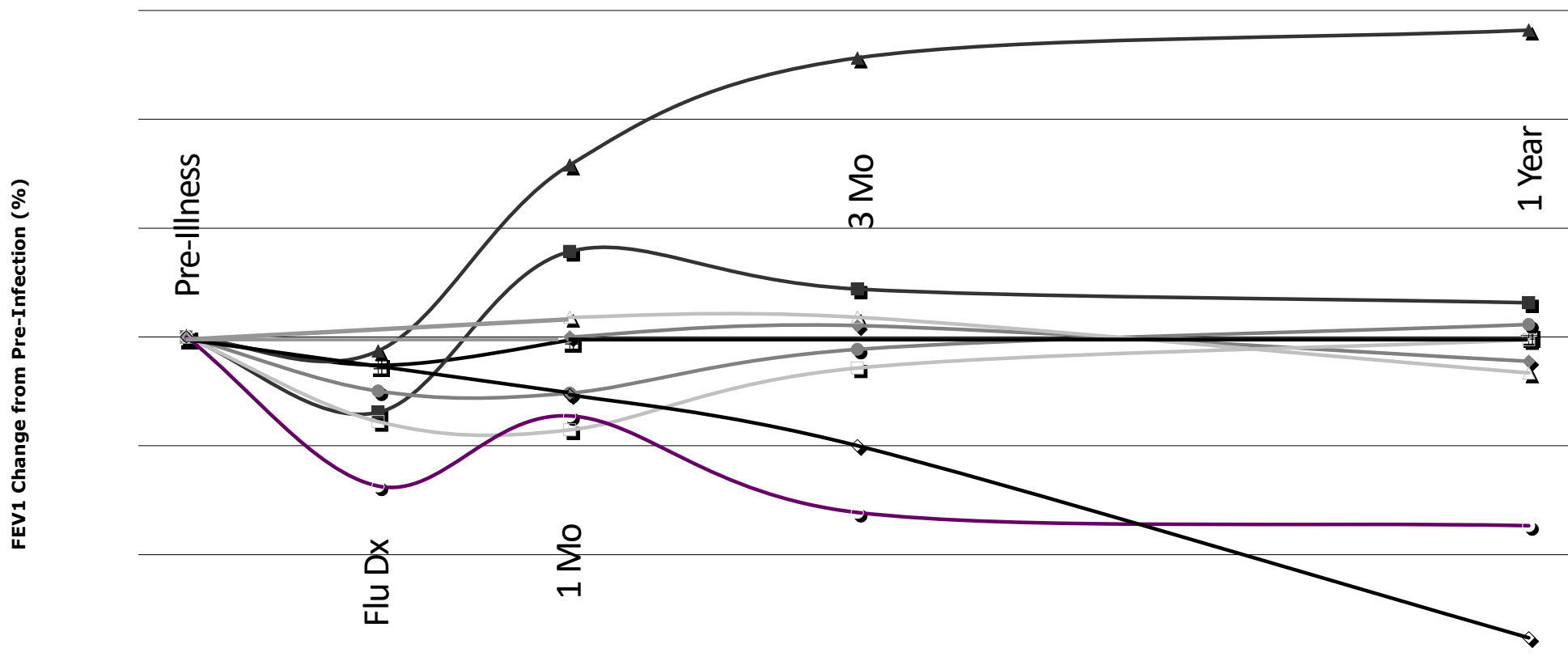
- Antiviral Therapy and Outcomes
 - No prospectively collected data
 - Most data with NAIs > M2 Inhibitors
 - Reduced mortality
 - M2 Inhibitors: 60% vs. 70%
 - NAI: Few deaths reported with use
 - Reduced viral shedding at day 10
 - M2 Inhibitors 20% vs. 50%
 - Lower rate of pneumonia
 - M2 inhibitors: 11% vs. 21%
 - NAI: 0-5% vs. 21%
 - Reduced risk of BOS
 - Risk of resistance emergence



Influenza: Virology in Setting of Treatment



Oseltamivir in Lung Transplantation: *PFT Effects*

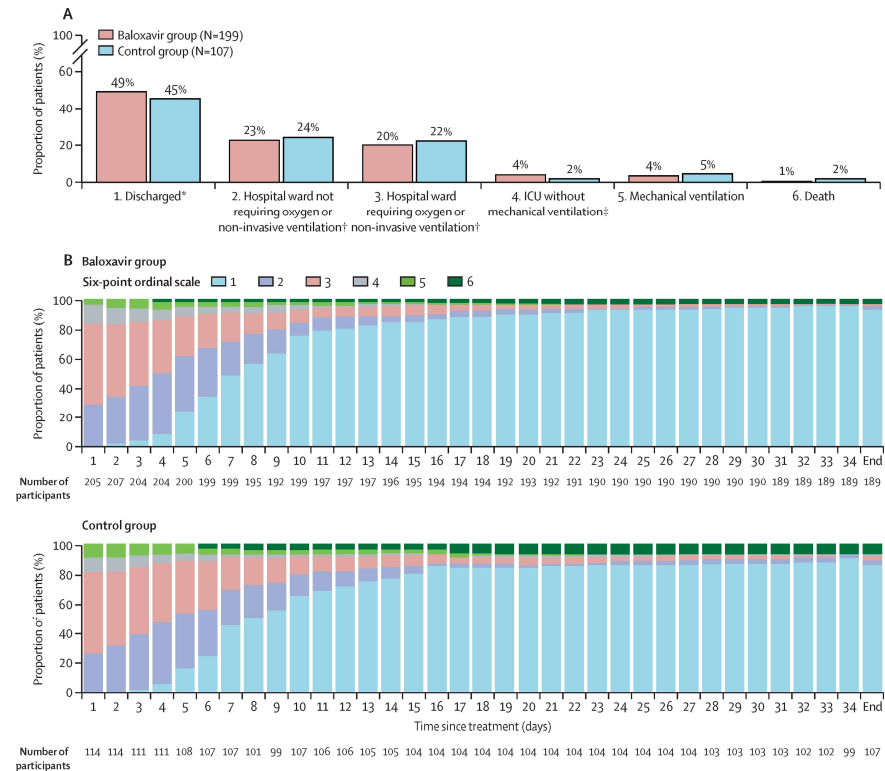
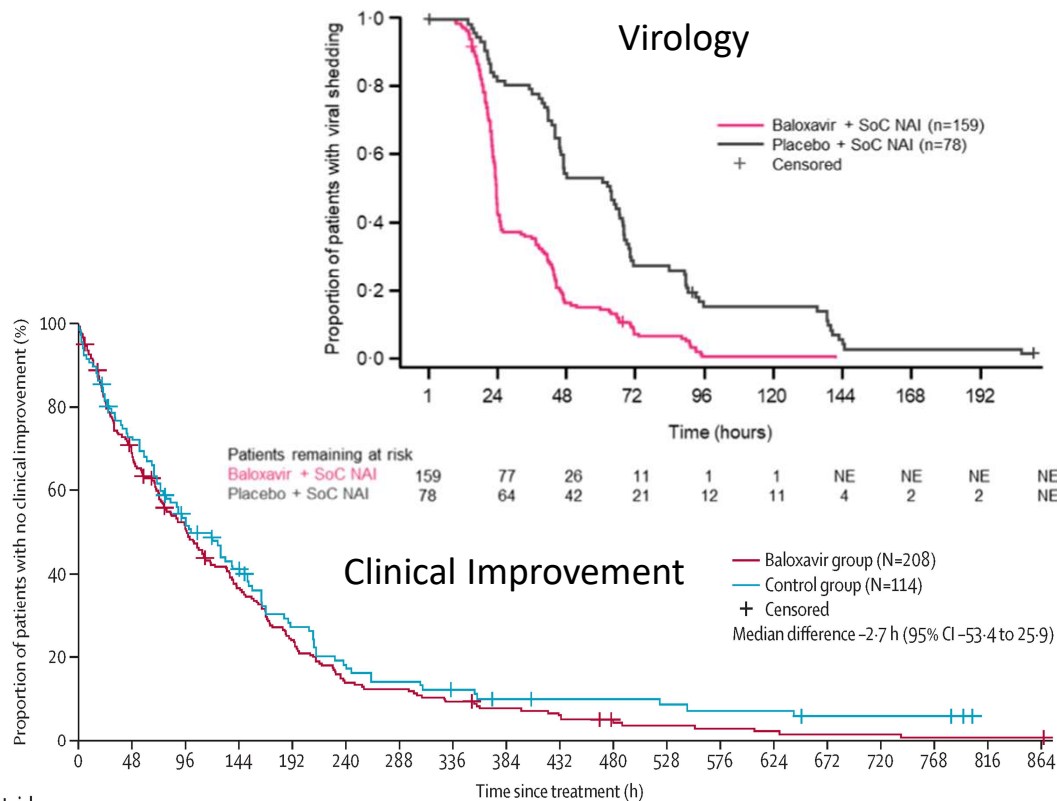


High Dose Oseltamivir: *Immunocompromised Patients*

Number (%) of patients with resistant virus detected	Conventional dose		Double dose	
	Adults (n = 73)	Children (< 18 years) (n = 8)	Adults (n = 78)	Children (< 18 years) (n = 8)
Resistance type				
Any resistance ^a	10/67 (15)	2/6 (33)	2/71 (3)	1/8 (13)
Phenotypic	6/62 (10)	2/6 (33)	1/62 (2)	0/8
Genotypic	7/64 (11)	2/5 (40)	2/68 (3)	1/8 (13)
Virus type ^b				
A (H1N1pdm2009)	4/16 (25)	1/1 (100)	1/13 (8)	1/1 (100)
A (H1N1)	1/2 (50)	0/0 (0)	0/1 (0)	0/0 (0)
A (H3N2)	3/29 (10)	1/3 (33)	1/33 (3)	0/4 (0)
B	2/20 (10)	0/2 (0)	0/24 (0)	0/3 (0)
Patient type ^{b, c}				
Hematopoietic stem cell transplant	4/9 (44)	1/2 (50)	1/13 (8)	0/0 (NE)
Solid organ transplant ^d	4/25 (16)	NE	1/22 (5)	NE
HIV infection	0/21 (0)	0/1 (0)	0/20 (0)	0/1 (0)
Systemic immunosuppressive immunotherapy	3/17 (18)	1/2 (50)	1/26 (4)	0/4 (0)
Hematologic malignancy	2/8 (25)	1/3 (33)	0/11 (0)	1/3 (33)

Combination Therapy for Hospitalized Adults

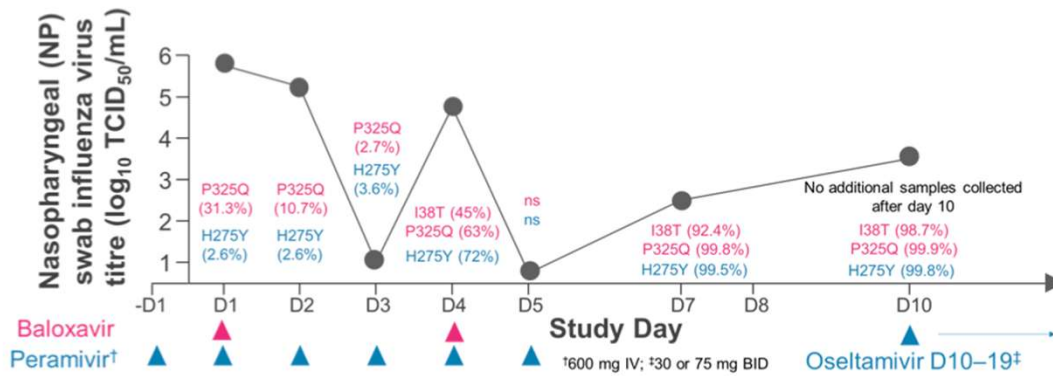
Ordinal Scale



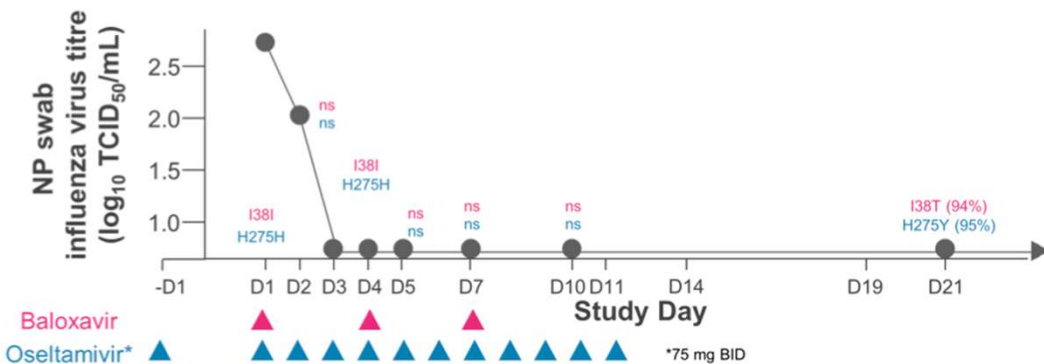
Number at risk (number censored)

	0	48	96	144	192	240	288	336	384	432	480	528	576	624	672	720	768	816	864
Baloxavir group	208 (0)	140 (3)	100 (7)	72 (8)	47 (8)	27 (8)	24 (8)	18 (8)	14 (9)	11 (9)	6 (11)	5 (11)	4 (11)	3 (11)	2 (11)	2 (11)	1 (11)	1 (11)	1 (11)
Control group	114 (0)	81 (2)	56 (4)	43 (6)	27 (8)	17 (8)	14 (8)	11 (9)	8 (10)	7 (11)	7 (11)	6 (11)	5 (11)	5 (11)	3 (12)	3 (12)	3 (12)	NE (NE)	NE (NE)

Combinations Prevent Resistance



(B)



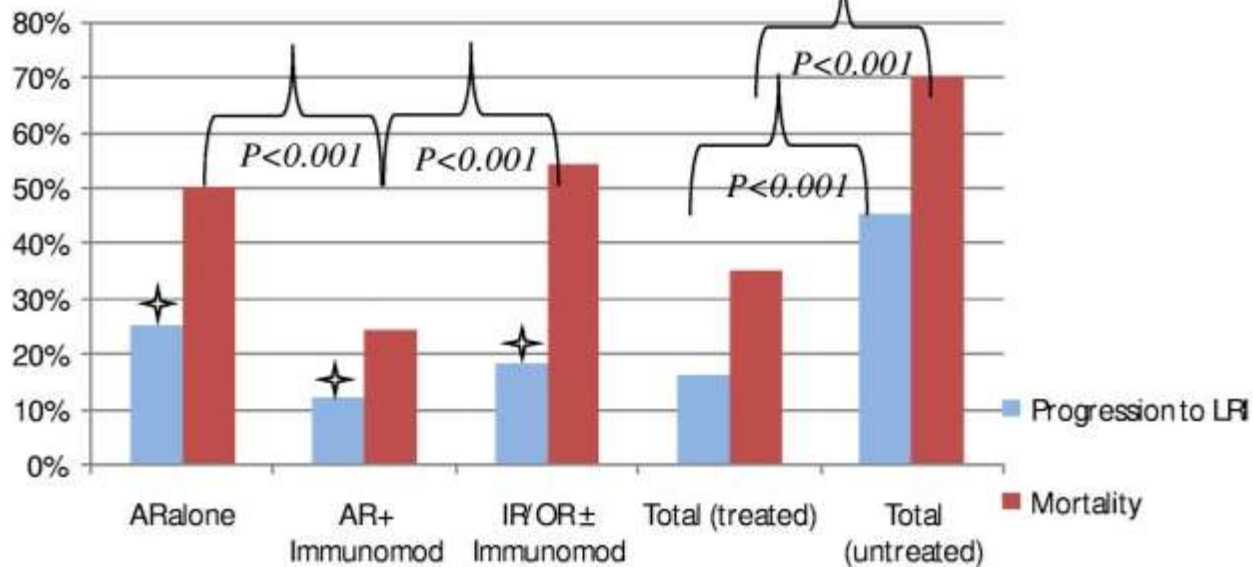
	Baloxavir + SoC NAI				Placebo + SoC NAI			
	A/H3N2	A/H1N1	B	Total	A/H3N2	A/H1N1	B	Total
Patients with paired sequences, n	58	64	12	134				
I38X	0	3 (4.7%)	0	3 (2.2%)	-	-	-	-
Patients with paired sequences, n	55	60	12	127	27	40	5	72
H275Y	0	2 (3.3%)	0	2 (1.6%)	0	3 (7.5%)	0	3 (4.2%)

Gaps and Endpoints: *Influenza*

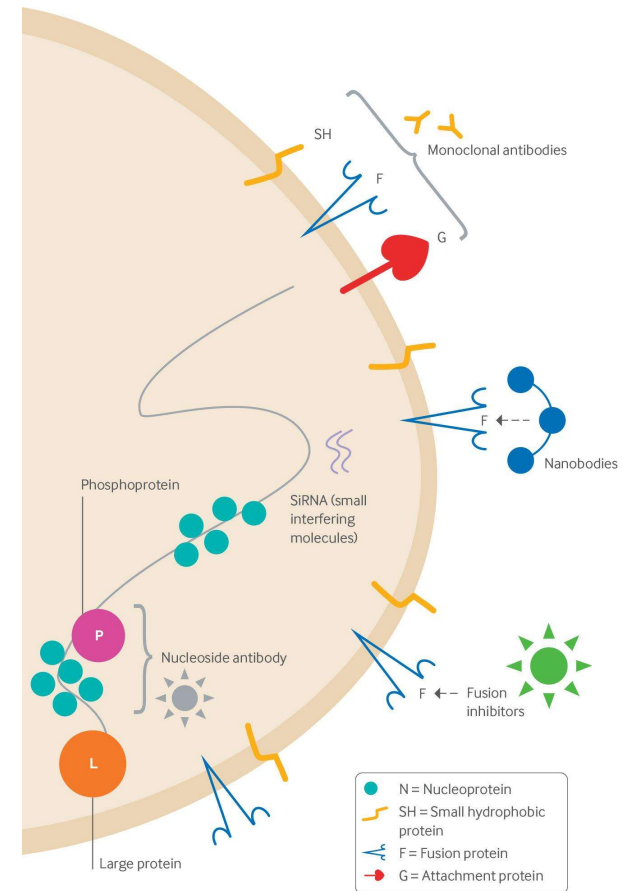
- Gaps
 - Management of hospitalized
 - Duration
 - Role of combination
 - Management of resistance
- Potential Endpoints
 - Virology does not correlate with clinical outcomes
 - Prevention of CLAD
 - Prevention of resistance?
 - DOOR endpoint
 - Ordinal Scale
 - PRO likely won't be useful in this population

RSV: Few Options, Mostly Directed at IC Hosts

Figure: Summary of outcome data by type of regimen received



✦ For progression to LRI: AR alone vs. AR plus immunomodulators or IR or OR with or without immunomodulators; $P=0.13$

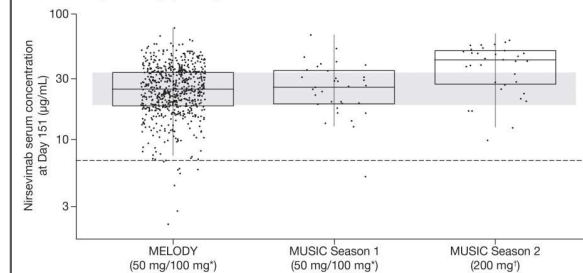


Promise of Monoclonal Antibodies: RSV

Analysis	Case Patients no. who received nirsevimab/total no. (%)	Control Patients no. who received nirsevimab/total no. (%)	Effectiveness (95% CI) percent
Primary analysis	60/690 (8.7)	97/345 (28.1)	83.0 (73.4 to 89.2)
Sensitivity analyses			
Previous nirsevimab receipt regardless of time	75/690 (10.9)	120/345 (34.8)	86.6 (78.8 to 91.5)
Bronchiolitis defined as the first wheezing attack	56/618 (9.1)	96/327 (29.4)	84.9 (75.4 to 90.7)
Propensity-score analysis	60/690 (8.7)	97/345 (28.1)	78.2 (65.7 to 86.2)
Multivariate model with complete case analysis	56/624 (9.0)	90/284 (31.7)	84.8 (74.9 to 90.7)
Multivariate model adjusted for previous RSV infection	60/690 (8.7)	97/345 (28.1)	83.1 (73.5 to 89.2)
Multivariate model adjusted for socioeconomic level	60/690 (8.7)	97/345 (28.1)	83.4 (73.8 to 89.4)
Multivariate conditional regression model including matching covariates	60/690 (8.7)	97/345 (28.1)	84.1 (74.9 to 90.0)
Standard logistic-regression model including unmatched patients	61/724 (8.4)	102/360 (28.3)	77.1 (67.4 to 84.0)
Multivariate model with gestational age at birth and birth weight as categorical variables	60/690 (8.7)	97/345 (28.1)	84.1 (74.9 to 90.0)
Subgroup analyses			
Age			
<3 mo	53/332 (16.0)	76/150 (50.7)	82.4 (69.3 to 89.9)
≥3 mo	7/358 (2.0)	21/195 (10.8)	82.7 (52.8 to 93.7)
≥1 Risk factor for severe bronchiolitis			
Yes	9/37 (24)	10/20 (50)	64.8 (-17.2 to 89.4)
No	50/623 (8.0)	83/295 (28.1)	78.2 (67.9 to 85.2)
RSV bronchiolitis with ventilatory support	27/189 (14.3)	46/151 (30.5)	67.2 (38.6 to 82.5)
RSV bronchiolitis with PICU admission	27/193 (14.0)	47/146 (32.2)	69.6 (42.9 to 83.8)

MUSIC Trial

Figure 1. Nirsevimab serum concentrations across MUSIC RSV Season 1 and RSV Season 2 compared with MELODY (as-treated population)



RVI in Lung Transplant: *Late Complications*

Respiratory Syncytial Virus, Human Metapneumovirus, and Parainfluenza Virus Infections in Lung Transplant Recipients: A Systematic Review of Outcomes and Treatment Strategies

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Background. Respiratory syncytial virus (RSV), parainfluenza virus (PIV), and human metapneumovirus (hMPV) are increasingly associated with chronic lung allograft dysfunction (CLAD) in lung transplant recipients (LTR). This systematic review primarily aimed to assess outcomes of RSV/PIV/hMPV infections in LTR and secondarily to assess evidence regarding the efficacy of ribavirin.

Methods. Relevant databases were queried and study outcomes extracted using a standardized method and summarized.

Results. Nineteen retrospective and 12 prospective studies were included (total 1060 cases). Pooled 30-day mortality was low (0–3%), but CLAD progression 180–360 days postinfection was substantial (pooled incidences 19–24%) and probably associated with severe infection. Ribavirin trended toward effectiveness for CLAD prevention in exploratory meta-analysis (odds ratio [OR] 0.61, [0.27–1.18]), although results were highly variable between studies.

Conclusions. RSV/PIV/hMPV infection was followed by a high CLAD incidence. Treatment options, including ribavirin, are limited. There is an urgent need for high-quality studies to provide better treatment options for these infections.

Keywords. lung transplantation; paramyxovirus; pneumovirus; ribavirin.

Oral Ribavirin: *Alveolar Lung Fluid Concentrations*

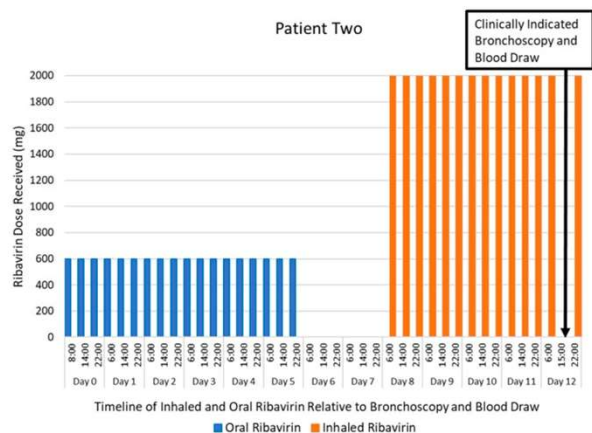
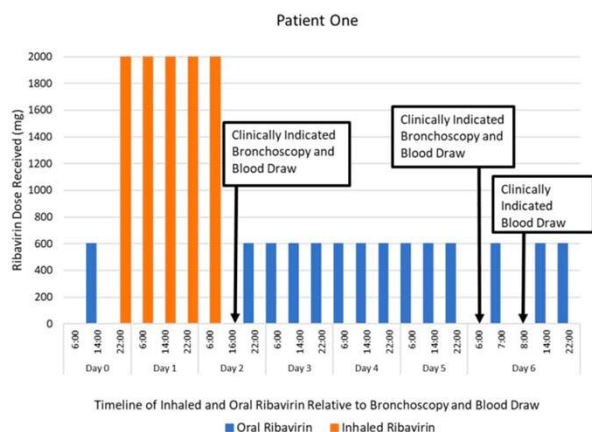


TABLE 1 Ribavirin and intracellular metabolite plasma and bronchoalveolar lavage concentrations

	Plasma ribavirin concentration	Blood RBC intracellular concentrations	Blood PBMC intracellular concentrations	BAL intracellular concentrations
Patient 1				
First sample (oral ribavirin followed by inhaled ribavirin)	0.473 µg/mL (trough)	Not available	Not available	iRTP: 6.32 pmol/10 ⁶ cells (15.3 µg/mL)
Second sample (inhaled ribavirin followed by oral ribavirin)	1.560 µg/mL (trough) and 2.210 µg/mL (peak)	Not available	Not available	iRTP: 3.43 pmol/10 ⁶ cells (8.3 µg/mL)
Patient 2				
First sample (oral ribavirin followed by inhaled ribavirin)	2.160 µg/mL (trough)	iRMP: 6.22 pmol/10 ⁶ cells (20.2 µg/mL)	iRMP: 1.17 pmol/10 ⁶ cells (1.9 µg/mL)	iRMP: 851 pmol/10 ⁶ cells (1379.0 µg/mL)
		iRDP: 14.3 pmol/10 ⁶ cells (57.8 µg/mL)	iRDP: 0.62 pmol/10 ⁶ cells (1.25 µg/mL)	iRDP: 41 pmol/10 ⁶ cells (82.9 µg/mL)
		iRTP: 31.3 pmol/10 ⁶ cells (151.5 µg/mL)	iRTP: 3.89 pmol/10 ⁶ cells (9.42 µg/mL)	iRTP: 103 pmol/10 ⁶ cells (249.0 µg/mL)

Abbreviations: iRMP, iRDP, iRTP, intracellular ribavirin mono-, di-, and tri-phosphate, respectively; PBMC, peripheral blood mononuclear cell; RBC, red blood cell.

IC₅₀ for Ribavirin vs RSV: 3-30 µg/mL

RSV01: Inhaled siRNA RSV Antiviral

Table 2 Disease Severity at Study Entry (Modified Intention-to-treat Cohort)

Parameter	Placebo (n = 33)	ALN-RSV01 (n = 44)	Overall (N = 77)
FEV ₁ change from pre-infection to screening ^a			
n	31	41	72
Mean (SD)	-14.6% (15.0%)	-11.6% (13.9%)	-12.9% (14.4%)
Median (IQR)	-13% (-26 to -2)	-9% (-16 to -2)	-10% (-22 to -2)
Lower respiratory symptoms [n (%)] ^b	22 (69)	30 (70)	52 (74)
Upper respiratory symptoms [n (%)] ^b	8 (25)	8 (19)	16 (21)
Chest X-ray or CT scan [n (%)] ^c			
Normal	12 (36)	10 (23)	22 (29)
Abnormal	20 (63)	34 (77)	54 (70)
Pretreatment symptom score			
Median (IQR)	6.0 (4.0–9.0)	5.0 (3.0–11.0)	6.0 (3.0–10.0)
Time from symptom onset to first dose [n (%)]			
< 5 days	7 (21)	12 (27)	19 (25)
≥ 5 days	26 (79)	32 (72)	58 (75)
RSV serotype [n (%)]			
N	28	42	70
Serotype A	15 (54)	21 (50)	36 (51)
Serotype B	13 (46)	21 (50)	34 (49)
RSV titer in log ₁₀ copies/ml [mean (SD)]			
Oropharyngeal wash	4 (1)	4 (2)	4 (1)
Nasal swab	7 (2)	7 (2)	7 (2)
RSV treatment [n (%)]			
Pulse steroids	19 (58)	31 (71)	50 (64)
Inhaled ribavarin	16 (49)	11 (25)	27 (35)
Oral ribavarin	7 (21)	11 (25)	18 (23)
Intravenous ribavarin	4 (12)	11 (25)	15 (19)
IVIg	4 (12)	4 (9)	8 (10)
Palivizumab	3 (9)	3 (7)	6 (8)

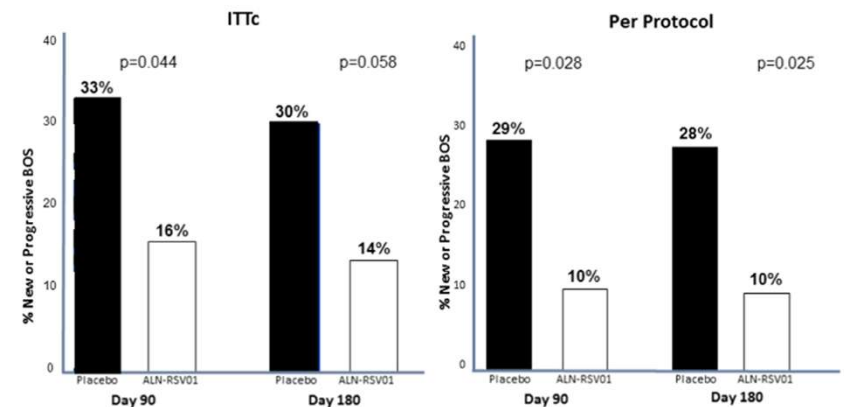
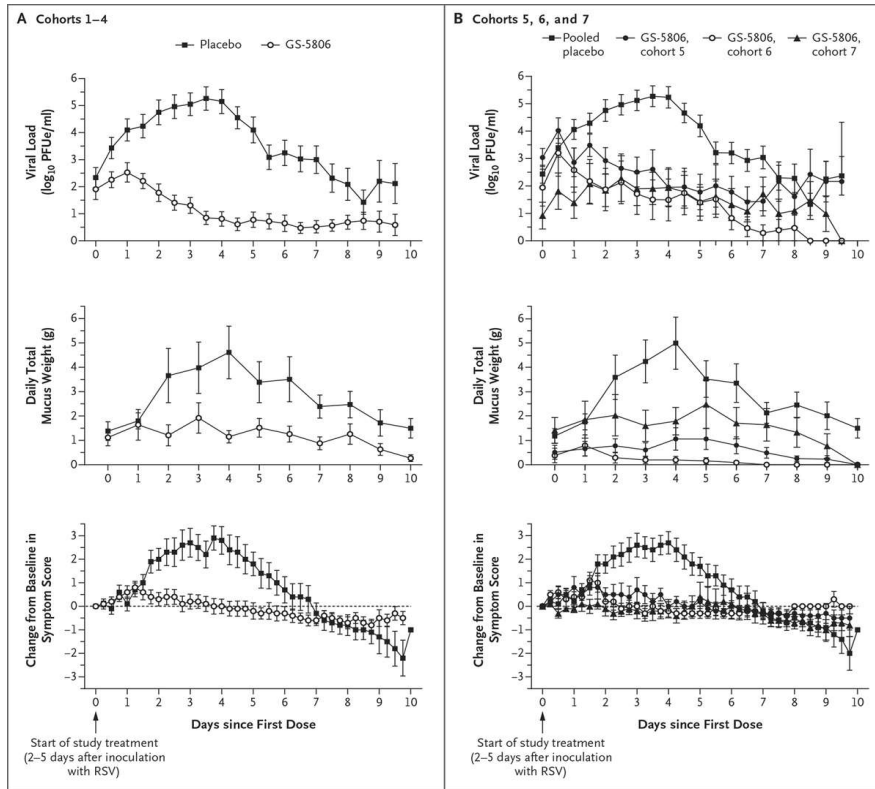


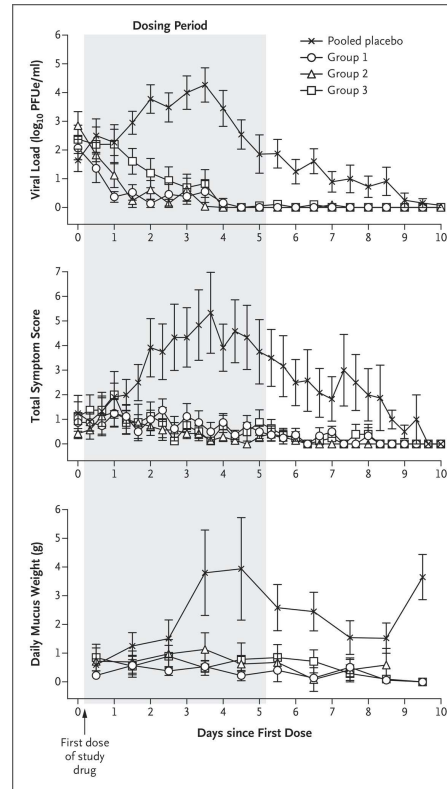
Figure 3 Incidence of new and progressive BOS in mITTc and PP populations. *p*-value from Cochran–Mantel–Haenszel (CMH) test adjusting for randomization strata.

Studied RSV Antivirals: Work in Challenge Model Studies but not in Patients

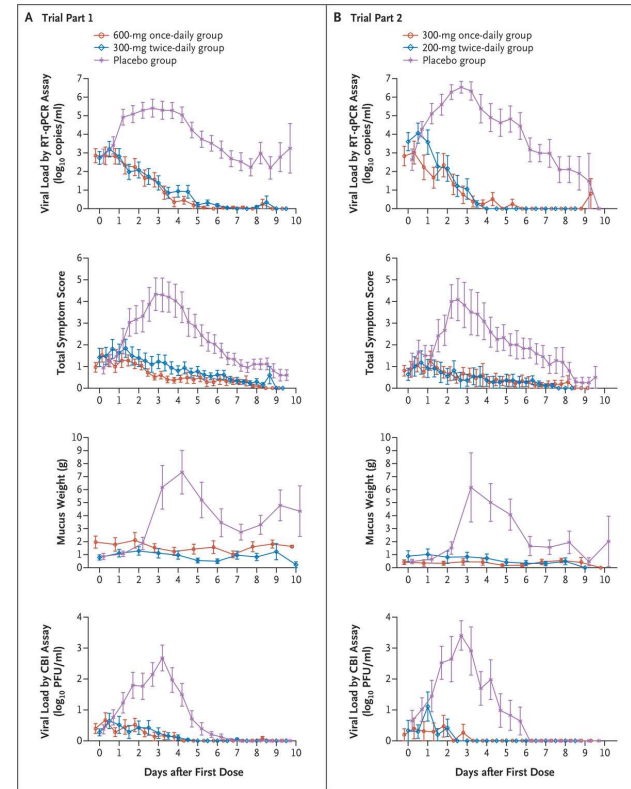
Presatovir F (Fusion) Inhibitor



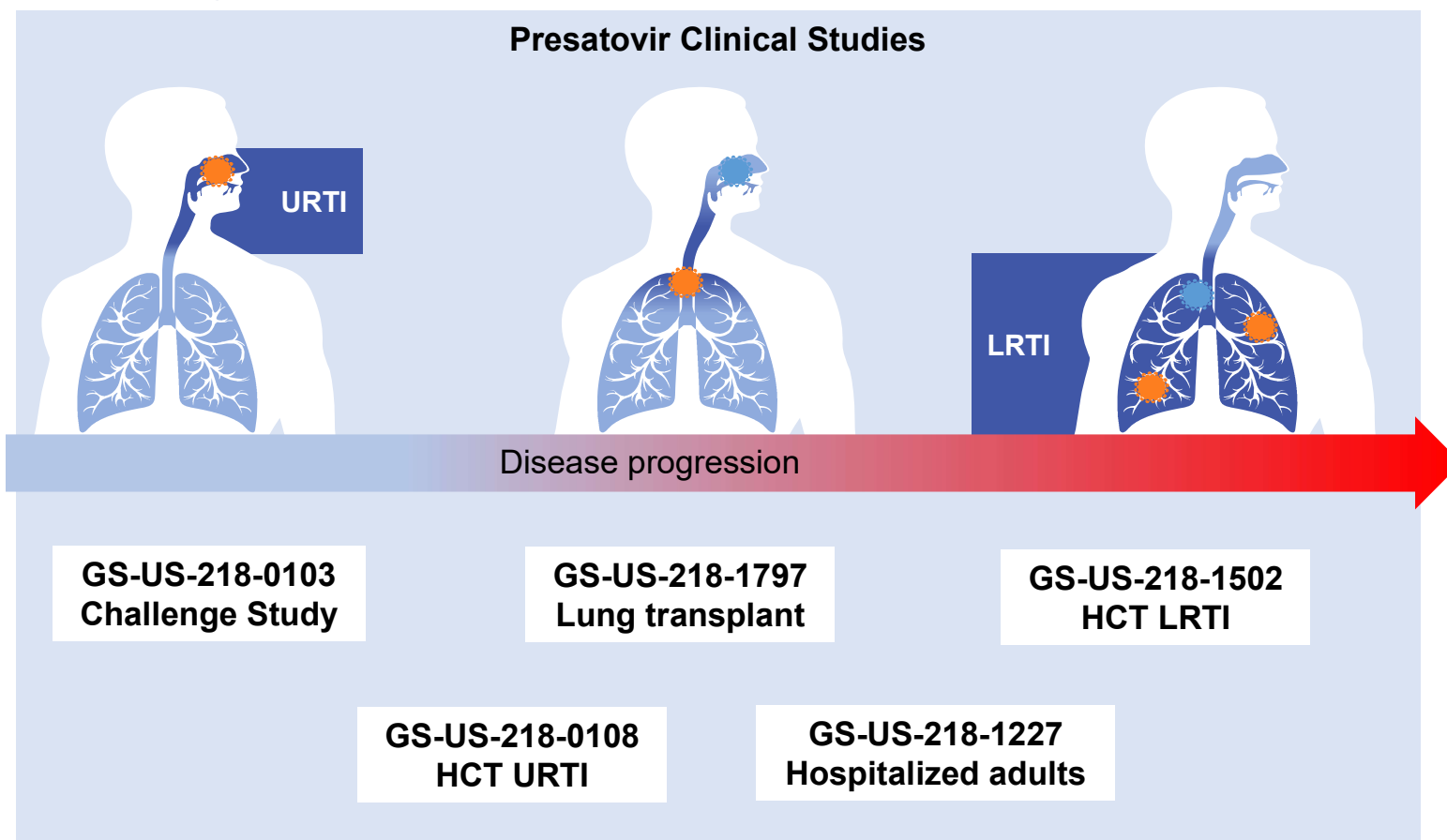
Lumicitabine Polymerase Inhibitor



EDP-938 N Protein Inhibitor

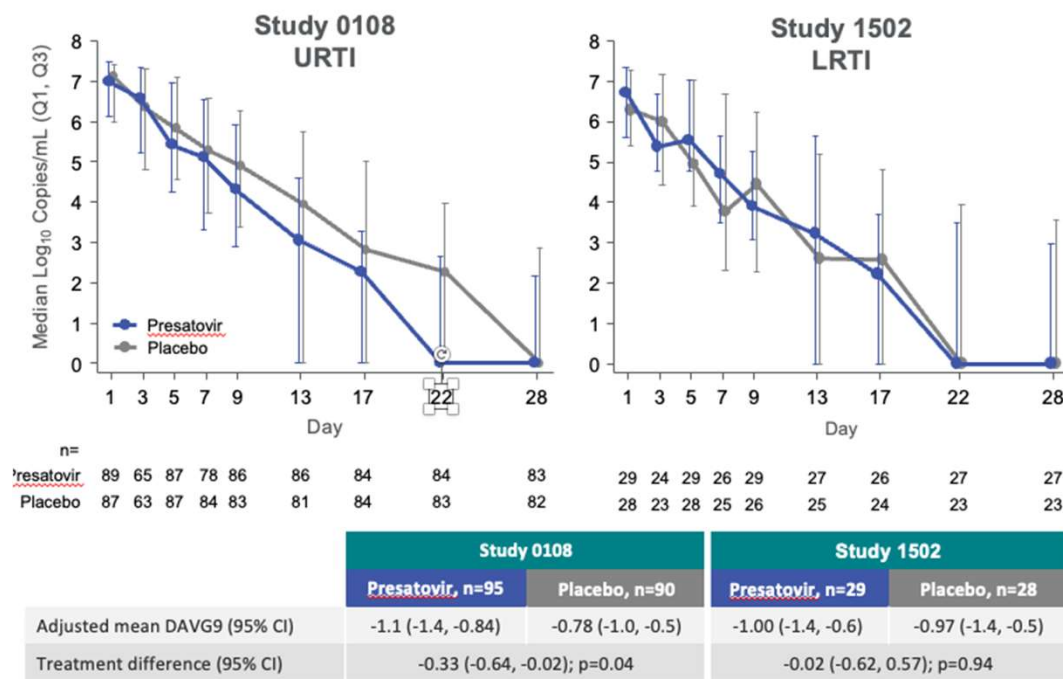


Summary of Presatovir Adult Phase 2 Studies

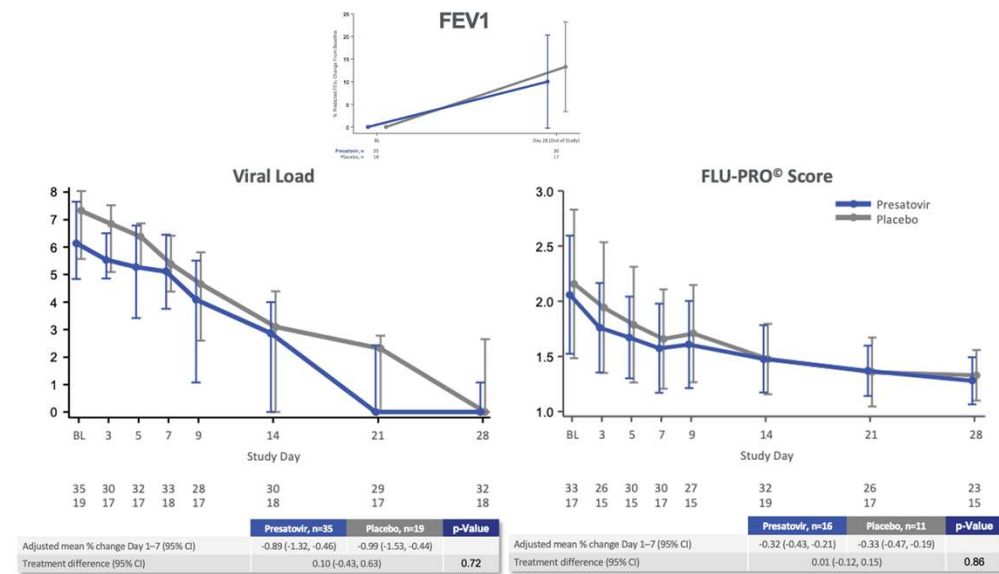


Studied RSV Antivirals: Work in Challenge Model Studies but not in Patients

HSCT Studies



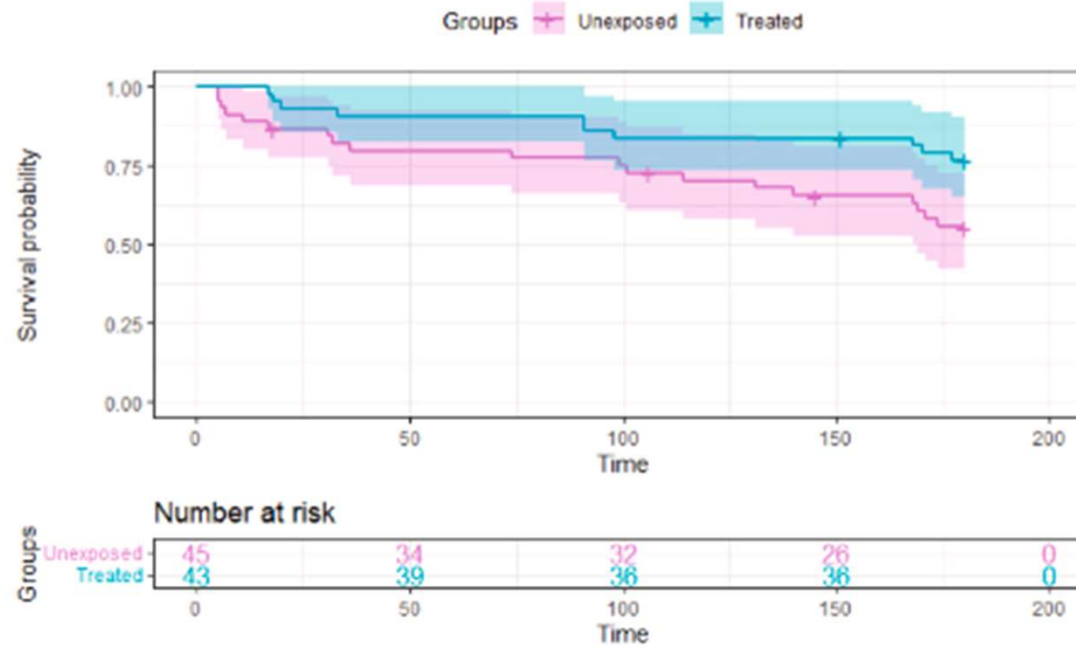
Lung Transplant Studies



Gaps and Endpoints: *RSV*

- Gaps
 - Risk and expected course
 - Role of Ribavirin
 - Role of immune modulation
- Potential Endpoints
 - Prevention of CLAD
 - DOOR endpoint
 - Ordinal Scale
 - Virology?

Promise of Monoclonal Antibodies: SARS-CoV-2



Log-rank test p-value=0.036

Continued Utility of Antivirals in ICH in Omicron Era

COVID-19-related hospitalization up to day 90

Table 2. Baseline demographic characteristics, comorbidities and SARS-CoV-2 treatment of hospitalized and non-hospitalized patients for COVID-19

	Overall	Hospitalized (n = 52)	Non-hospitalized (n = 358)	OR (95% CI)	P value
Demographics					
Age (years), median (IQR)	57.5 (47–68)	63 (55–77)	56 (46–67)	1.04 (1.02–1.68)	<0.001
Age ≥ 65 years	32.4 (133/410)	46.2 (24/52)	30.4 (109/358)	1.95 (1–08–3.53)	0.024
Sex female	53.2 (218/410)	42.3 (22/52)	57.7 (30/358)	0.91 (0.86–1.12)	0.093
Vaccination					
Vaccination > 2 doses	2.9 (12/410)	5.8 (3/52)	2.5 (9/352)	0.42 (0.11–1.2)	0.185
Days from last doses vaccine to disease, median (IQR)	124 (77–190)	131 (94–193)	124 (77–188.5)	1.00 (0.99–1.00)	0.317
Days from last doses vaccine to disease ≥ 180 days	71.1 (286/402)	36.0 (18/50)	27.8 (98/352)	1.45 (0.78–2.71)	0.233
Comorbidities					
Hypertension	39.8 (163/410)	51.9 (27/52)	38.0 (136/358)	1.76 (0.98–3.21)	0.055
Chemotherapy	20 (82/410)	23.1 (12/52)	19.6 (70/358)	1.24 (0.61–2.47)	0.553
Diabetes mellitus	19.3 (32/410)	23.1 (12/52)	18.7 (67/358)	1.30 (0.65–2.61)	0.456
Transplantation	13.4 (55/410)	11.5 (6/52)	13.7 (49/358)	0.82 (0.33–2.03)	0.671
Cardiovascular disease	12.4 (51/410)	23.1 (12/52)	10.9 (39/358)	2.45 (1.18–5.07)	0.013
Cerebrovascular disease	13.9 (6/410)	5.8 (3/52)	3.6 (13/358)	1.65 (0.44–5.90)	0.457
eGFR < 30 mL/min	4.4 (18/410)	7.7 (4/52)	3.9 (14/358)	2.05 (0.65–6.48)	0.214
Pulmonary chronic disease	3.4 (14/410)	9.6 (5/52)	2.5 (9/358)	4.12 (1.32–12.83)	0.014
Haemodialysis	1.2 (5/410)	3.8 (2/52)	0.8 (3/358)	4.73 (0.72–29.02)	0.123
Categories					
Transplantation	15.6 (64/410)	15.4 (8/52)	15.6 (56/358)	1	
Immunomodulatory therapy ^a	37.1 (152/410)	11.5 (6/52)	40.8 (146/358)	0.28 (0.09–0.86)	0.027
Anti-CD20	27.3 (112/410)	50.0 (26/52)	24.0 (86/358)	2.12 (0.89–5.01)	0.088
Chemotherapy	20.0 (82/410)	14.6 (12/52)	19.6 (70/358)	1.20 (0.45–3.13)	0.710
SARS-CoV-2 treatment					
Days from symptom to treatment, median (IQR)	4 (2.2–5)	5.5 (3.5–7.5)	4 (2–5)	1.00 (0.94–1.07)	0.078
Days from symptom to treatment ≥ 4 days	52.7 (108/205)	75.0 (6/8)	51.8 (102/197)	2.79 (0.55–14.18)	0.285
Treatment exposed ^b	50 (205/410)	15.4 (8/52)	55 (197/358)	0.15 (0.07–0.33)	<0.001
Remdesivir	32 (131/410)	5.8 (3/52)	35.8 (128/358)	0.11 (0.34–0.36)	<0.001
Sotrovimab	12.7 (52/410)	5.8 (3/52)	13.7 (49/358)	0.38 (0.11–1.28)	0.110
Nirmatrelvir/ritonavir	3.2 (13/410)	(0/51)	3.6 (13/358)	NA	0.387

Risk Factor

	Odds Ratio (95% CI)	P
≥65 years of age	2.05 (1.02–4.15)	0.044
Biological immunomodulators	0.27 (0.10–0.74)	0.011
Anti-CD20-mediated B cell depletion	2.76 (1.31–5.82)	0.008
Cardiovascular disease	2.11 (0.84–5.31)	0.113
OCFA	4.65 (1.09–19.69)	0.037
Antiviral use	0.13 (0.05–0.29)	0.000

COVID-19-related hospitalization up to day 90

Risk Factor

	Odds Ratio (95% CI)	P
≥65 years of age	1.92 (0.98–3.79)	0.058
Biological immunomodulators	0.31 (0.11–0.83)	0.020
Anti-CD20-mediated B cell depletion	2.01 (1.01–4.29)	0.046
Cardiovascular disease	2.40 (0.97–5.92)	0.057
OCFA	4.81 (1.23–18.77)	0.024
Remdesivir use	0.13 (0.04–0.44)	0.001

COVID-19 Treatment Guidelines

Patient Disposition	Panel's Recommendations
All Patients	- Symptom management should be initiated for all patients (AIII). - The Panel recommends against the use of dexamethasone^a or other systemic corticosteroids (AIIb), unless these agents are being used to treat an underlying condition (AIII).
Patients Who Are at High Risk of Progressing to Severe COVID-19 ^{b,c,d}	<i>Preferred therapies. Listed in order of preference:</i> Ritonavir-boosted nirmatrelvir (Paxlovid)^e (AIIa). Start as soon as possible and within 5 days of symptom onset. See footnote on drug-drug interactions.^f Remdesivir^{g,h} (BIIa). Start as soon as possible and within 7 days of symptom onset. <i>Alternative therapy. For use when the preferred therapies are not available, feasible to use, or clinically appropriate.^h</i> Molnupiravir^{g,i} (CIIa). Start as soon as possible and within 5 days of symptom onset. There is insufficient evidence for the Panel to recommend either for or against initiating these antiviral agents after the timeframes listed above. Each recommendation in the Guidelines receives a rating for the strength of the recommendation (A, B, or C) and a rating for the evidence that supports it (I, IIa, IIb, or III). See Guidelines Development for more information.

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy		Recommendations for Anticoagulant Therapy
	Clinical Scenario	Recommendation	
Hospitalized for Reasons Other Than COVID-19	Patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19 ^a	See Therapeutic Management of Nonhospitalized Adults With COVID-19 . ^b	For patients without an indication for therapeutic anticoagulation: Prophylactic dose of heparin, unless contraindicated (AI); (BIII) for pregnant patients
Hospitalized but Does Not Require Supplemental Oxygen	All patients	The Panel recommends against the use of dexamethasone (AIIa) or other systemic corticosteroids (AIIb) for the treatment of COVID-19. ^c	
	Patients who are at high risk of progressing to severe COVID-19 ^a	Remdesivir ^d (BIIb) for patients who are immunocompromised; (BIII) for other high-risk patients	
Hospitalized and Requires Conventional Oxygen ^a	Patients who require minimal conventional oxygen	Remdesivir ^{d,e} (BIIa)	For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk: Therapeutic dose of heparin^g (CIIa)
	Most patients	Use dexamethasone plus remdesivir ^d (BIIa). If remdesivir cannot be obtained, use dexamethasone (BI).	
	Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation	Add 1 of the following immunomodulators: ^g <i>Preferred</i> PO baricitinib (BIIa) IV tocilizumab (BIIa) <i>Alternatives (Listed in Alphabetical Order)</i> IV abatacept (CIIa) IV infliximab (CIIa)	For other patients: Prophylactic dose of heparin, unless contraindicated (AI); (BIII) for pregnant patients
Hospitalized and Requires HFNC Oxygen or NIV	All patients	Dexamethasone should be administered to all patients (AI). If not already initiated, promptly add 1 of the following immunomodulators: ^{h,i} <i>Preferred</i> PO baricitinib (AI) <i>Preferred Alternative</i> IV tocilizumab (BIIa) <i>Additional Alternatives (Listed in Alphabetical Order)</i> IV abatacept (CIIa) IV infliximab (CIIa) Add remdesivir to 1 of the options above in certain patients (for examples, see footnote). ^j	For patients without an indication for therapeutic anticoagulation: Prophylactic dose of heparin, unless contraindicated (AI); (BIII) for pregnant patients For patients who start on a therapeutic dose of heparin in a non-ICU setting and then transfer to the ICU, the Panel recommends switching to a prophylactic dose of heparin , unless there is another indication for therapeutic anticoagulation (BIII).
Hospitalized and Requires MV or ECMO	All patients	Dexamethasone should be administered to all patients (AI). If the patient has not already received a second immunomodulator, promptly add 1 of the following (listed in alphabetical order): ^{k,l} PO baricitinib^m (BIIa) IV tocilizumabⁿ (BIIa) See footnote k for a discussion on the use of remdesivir.	

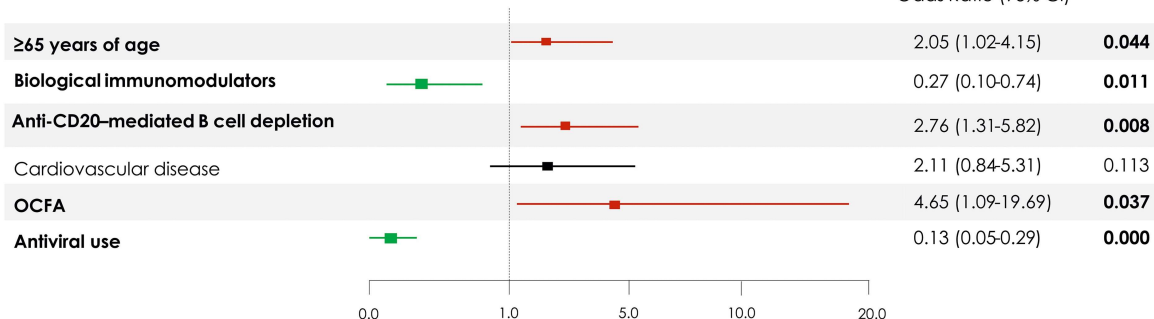
Continued Utility of Antivirals in ICH in Omicron Era

COVID-19-related hospitalization up to day 90

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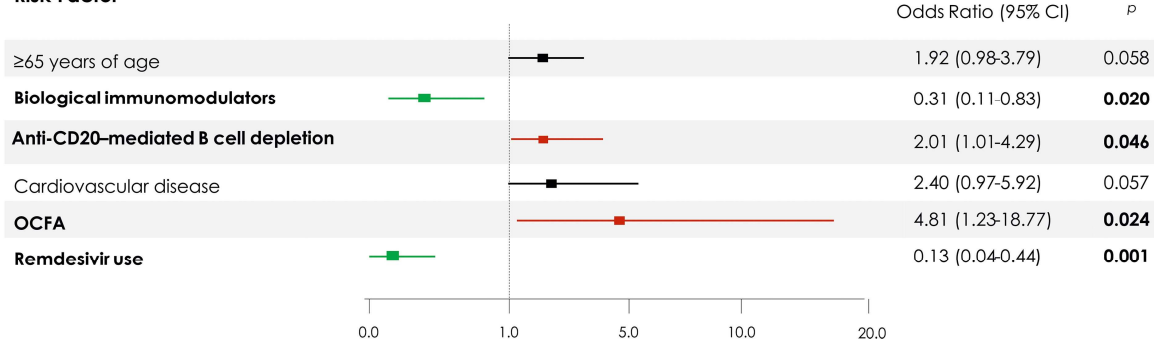
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Risk Factor



COVID-19-related hospitalization up to day 90

Risk Factor

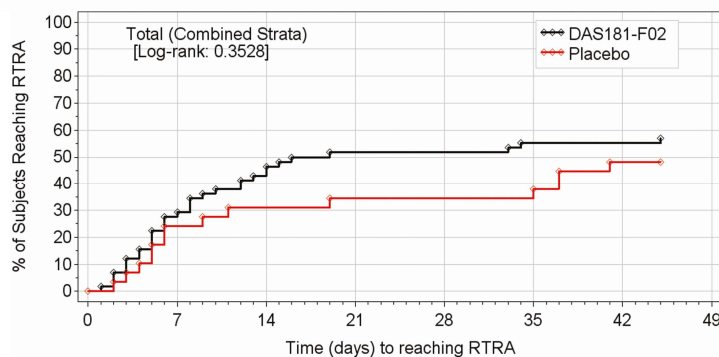
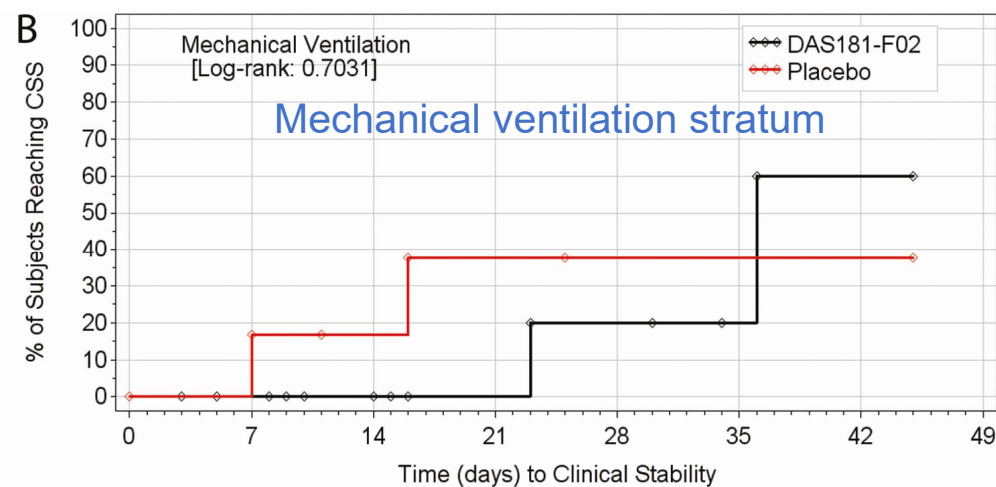
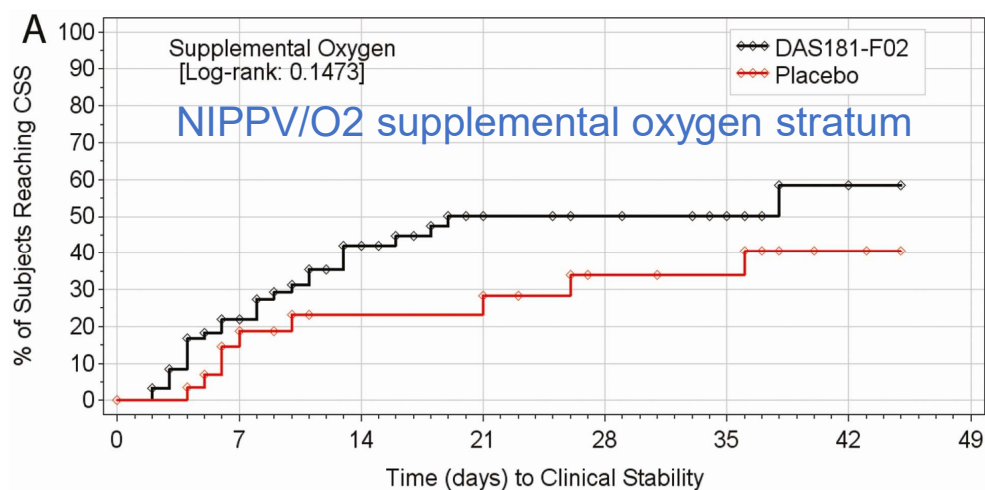


PIV in Transplantation: *Ribavirin ± Immunoglobulin*

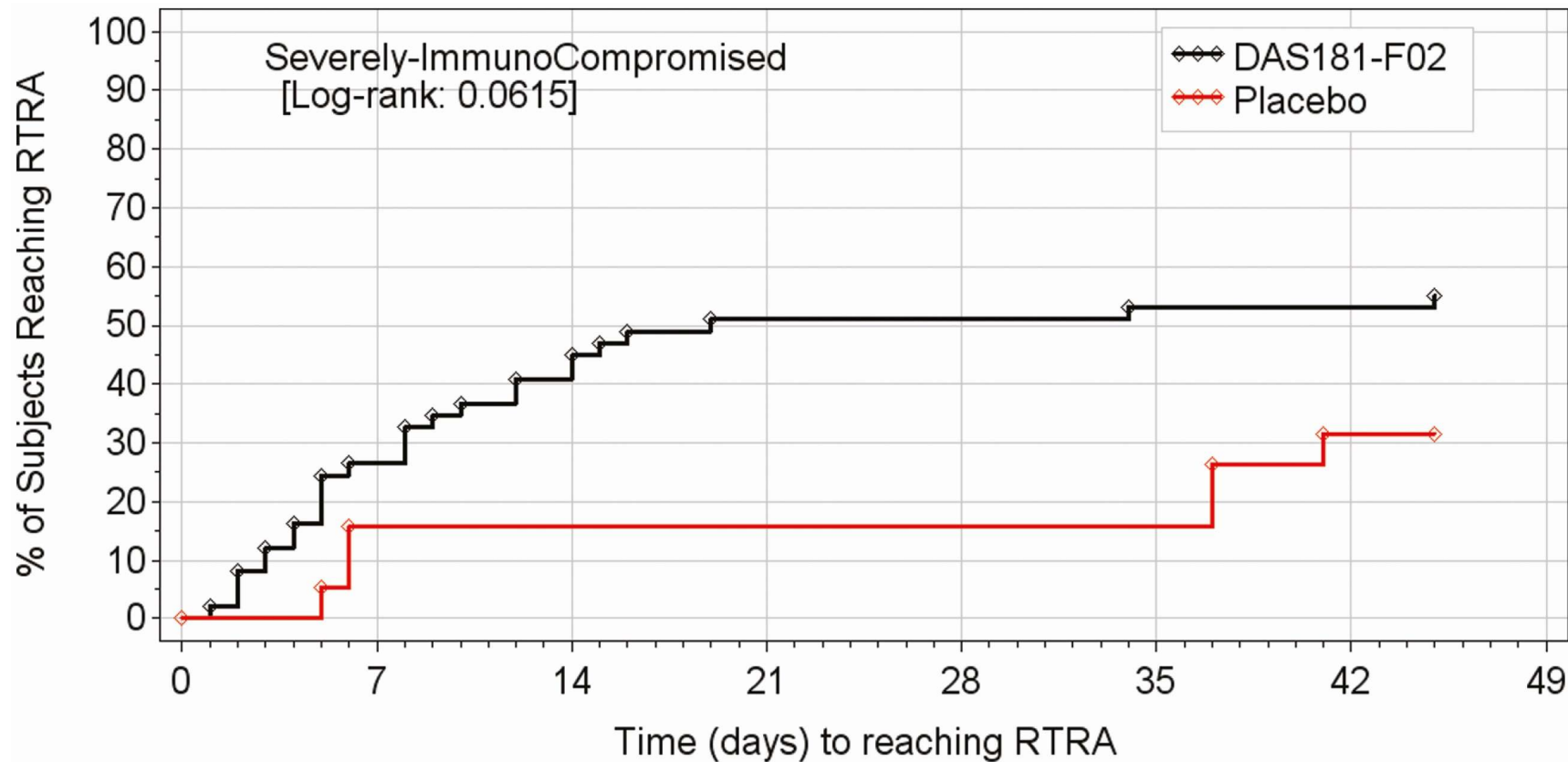
Table 3. Outcome of Ribavirin Treatment in Treated Versus Untreated Immunocompromised Patients^a

Study	Serotype	Symptoms	Route of Administration	Outcome, No. Survived/No. Treated
Wendt et al (1992) [43]	NA	LRTI/URTI	Aerosolized	7/9
	NA	LRTI/URTI	None	14/18
Elizaga et al (2001) [44]	PIV-3	URTI	Aerosolized	8/8
	PIV-3	LRTI	Aerosolized	4/10
	NA	LRTI	None	4/4
Nichols et al (2001) [45]	PIV-3	LRTI	Aerosolized with or without IVIG	11/31 (35%) shed virus 21 d after treatment
	PIV-3	LRTI	None	8/24 (33%) shed virus 21 d after treatment
Dignan et al (2006) [46]	PIV-3	LRTI	Aerosolized/intravenous	5/6
	PIV-3	LRTI	None	4/6
	PIV-3	URTI	Aerosolized/intravenous	2/2
	PIV-3	URTI	None	8/9
Chemaly et al (2014) [47]	PIV-3	LRTI/URTI	Aerosolized	8/9
	PIV-3	LRTI/URTI	None	58/65
Total	...	...	Aerosolized	34/44 (77.3%)
			None	88/102 (86.3%)

DAS181 For the Treatment of Parainfluenza Virus: *Results*



DAS181 For the Treatment of Parainfluenza Virus: *Results*

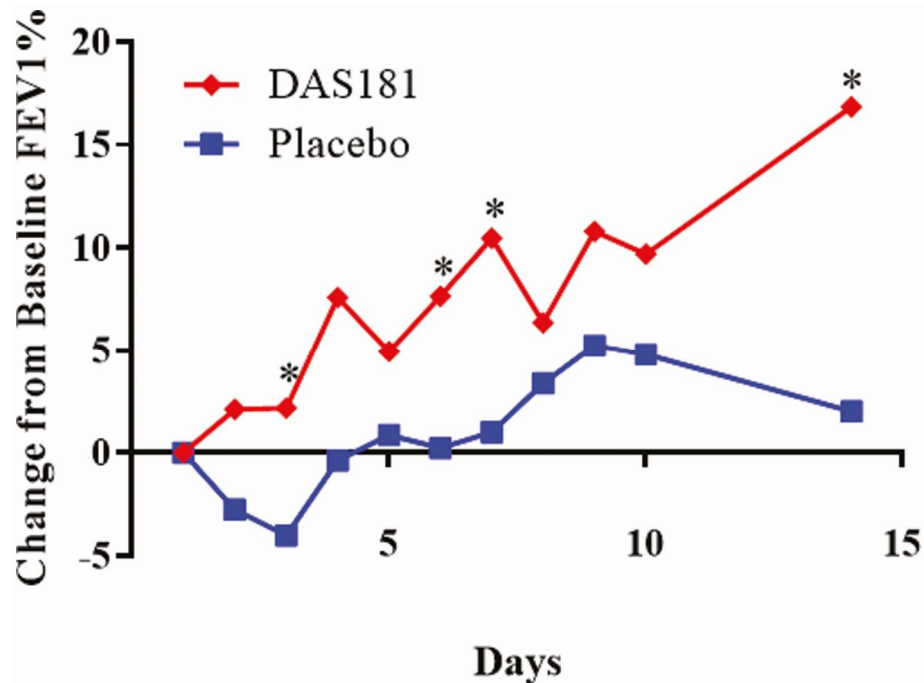


Gaps and Endpoints: *PIV*

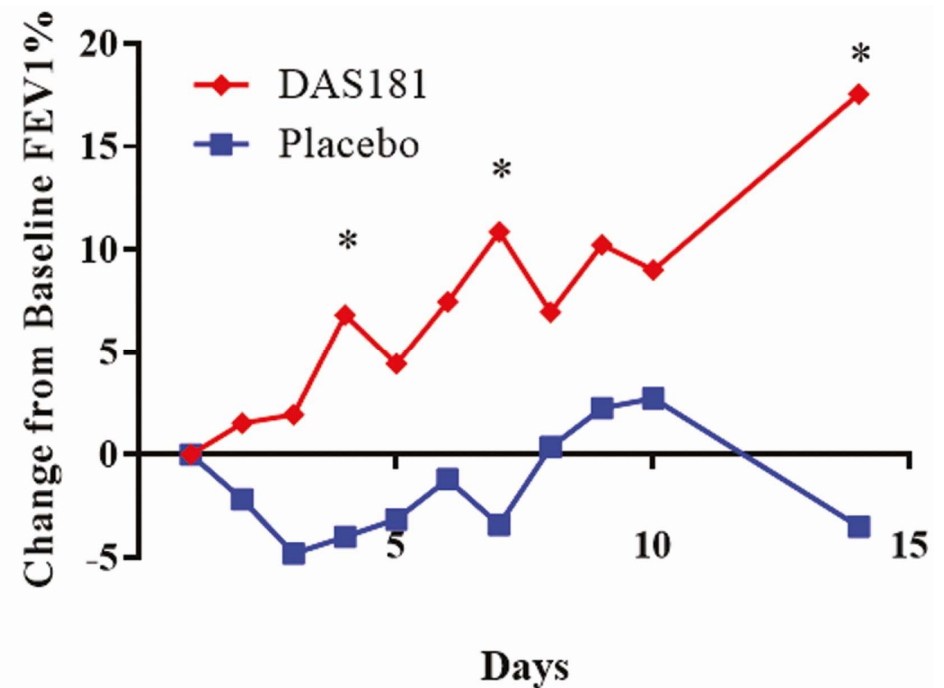
- Gaps
 - Risk and expected course
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DAS181 For the Treatment of Parainfluenza Virus: *Results*

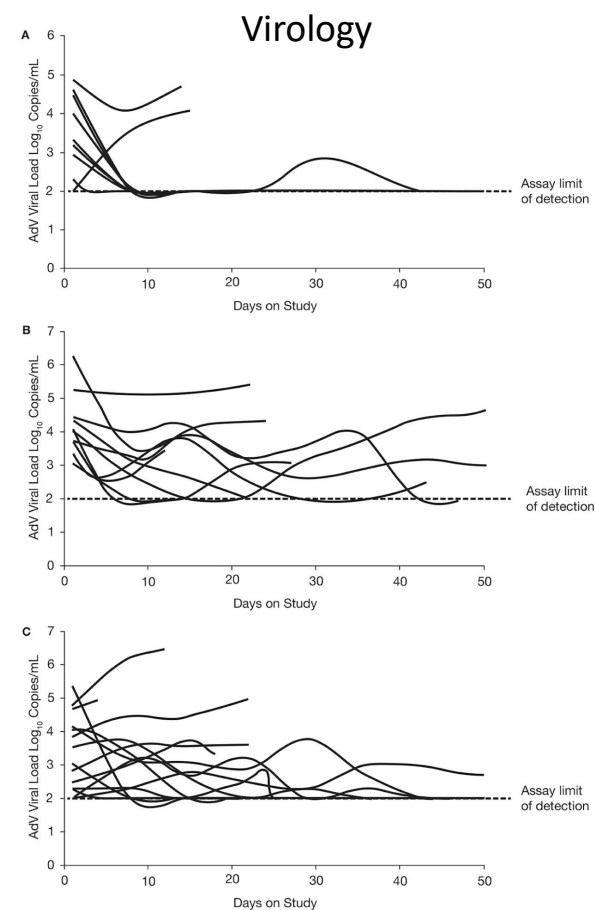
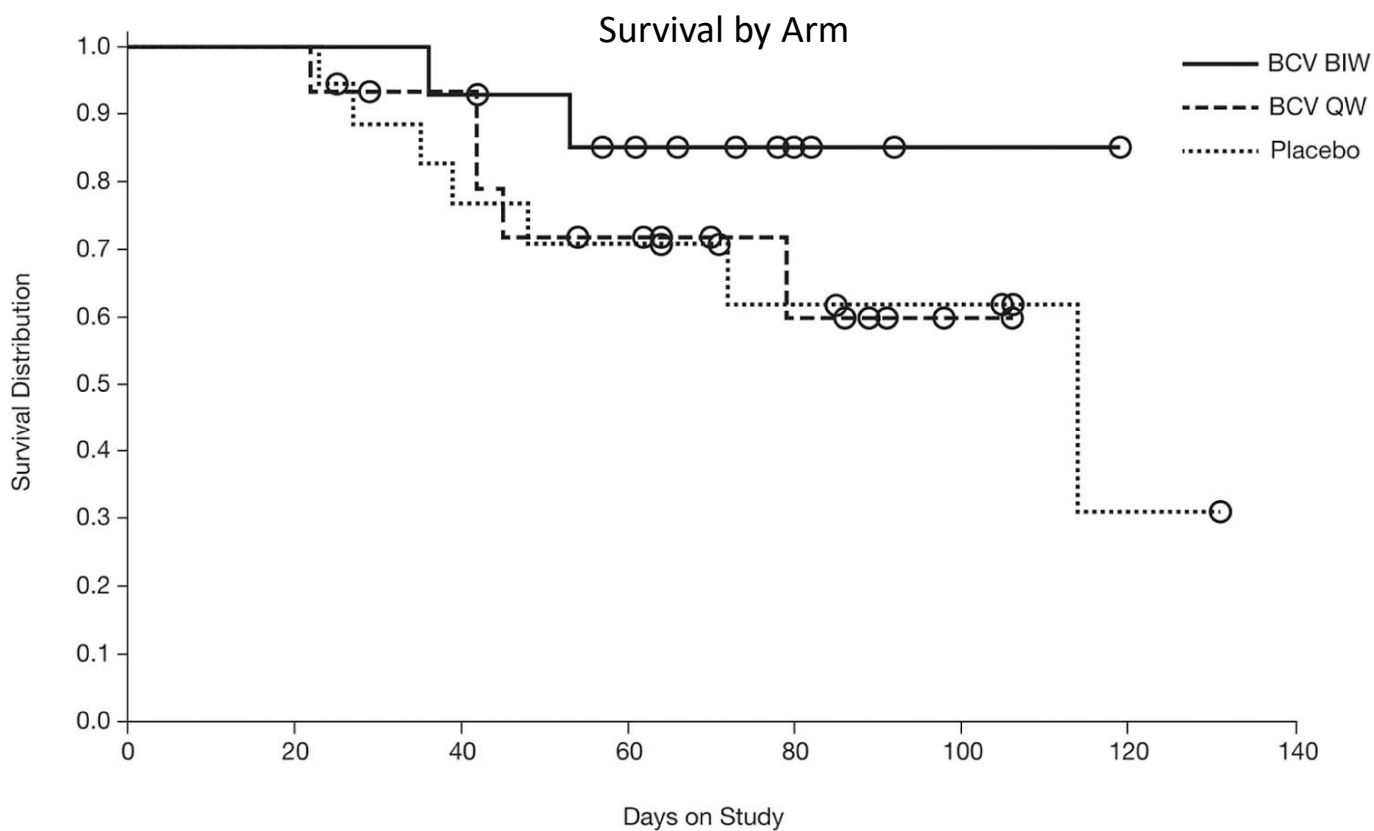
All Subjects



Severely Immunocompromised



Brincidofovir and Adenovirus



Questions?

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