

ADENOVIRUS VIRAL BURDEN IS ASSOCIATED WITH MORTALITY IN PEDIATRIC ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT RECIPIENTS: RESULTS FROM THE ADVANCE STUDY

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⁷Analytica-Laser, New York, NY, United States

Disclosures

- ⦿ MZ, KR, APM, CP, and SV are investigators in the AdVance study sponsored by Chimerix
- ⦿ EV, TB, EM, and GN are employees of the study sponsor, Chimerix
- ⦿ AC is an employee of Analytica-Laser, a research consultancy who conducted the study on behalf of the sponsor, Chimerix

Rationale for the AdVance study

- ⚙️ There is a lack of detailed, multicenter data collected using consistent methodology on standards of care, disease course, and outcomes in patients with adenovirus (AdV) post-allogeneic HCT
- ⚙️ Despite published data on the high risk of morbidity and mortality with AdV infection (most from the single-center experience),¹⁻³ the literature is difficult to interpret due to the lack of clear definitions regarding various stages of infection
- ⚙️ No clear correlation between virology parameters, response to antiviral therapy, and comorbidities/outcomes has been established

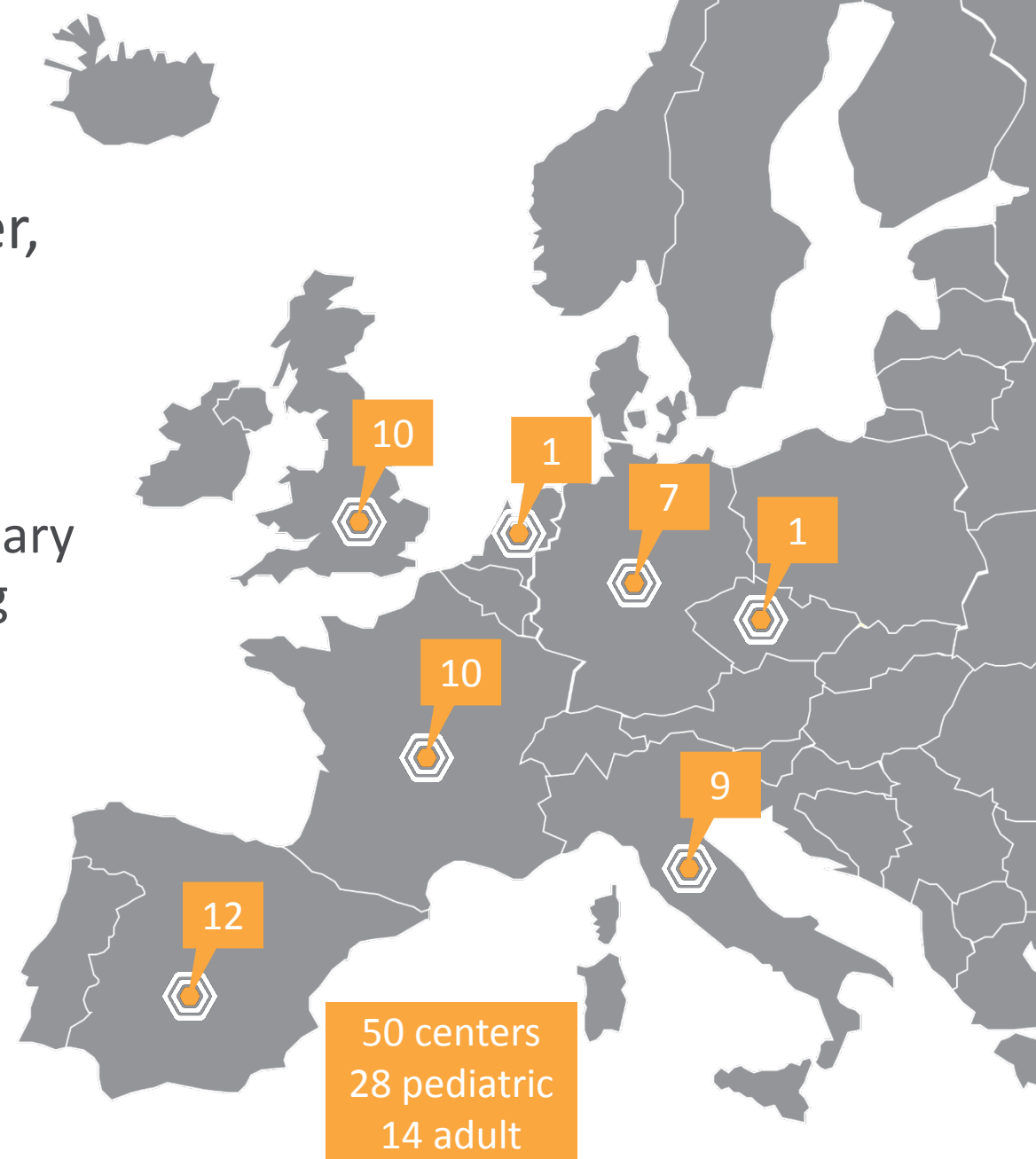
¹Hutspardol S et al. *Biol Blood Marrow Transplant*. 2015;21:1802-7. ²Yilmaz M et al. *Bone Marrow Transplant*. 2013;48:1218-23.

³Taniguchi K et al. *Ann Hematol*. 2012;91:1305-12.

The AdVance study

AdVance is a retrospective, multicenter, multinational study of the incidence, management, and clinical outcomes of AdV infection in allo-HCT recipients

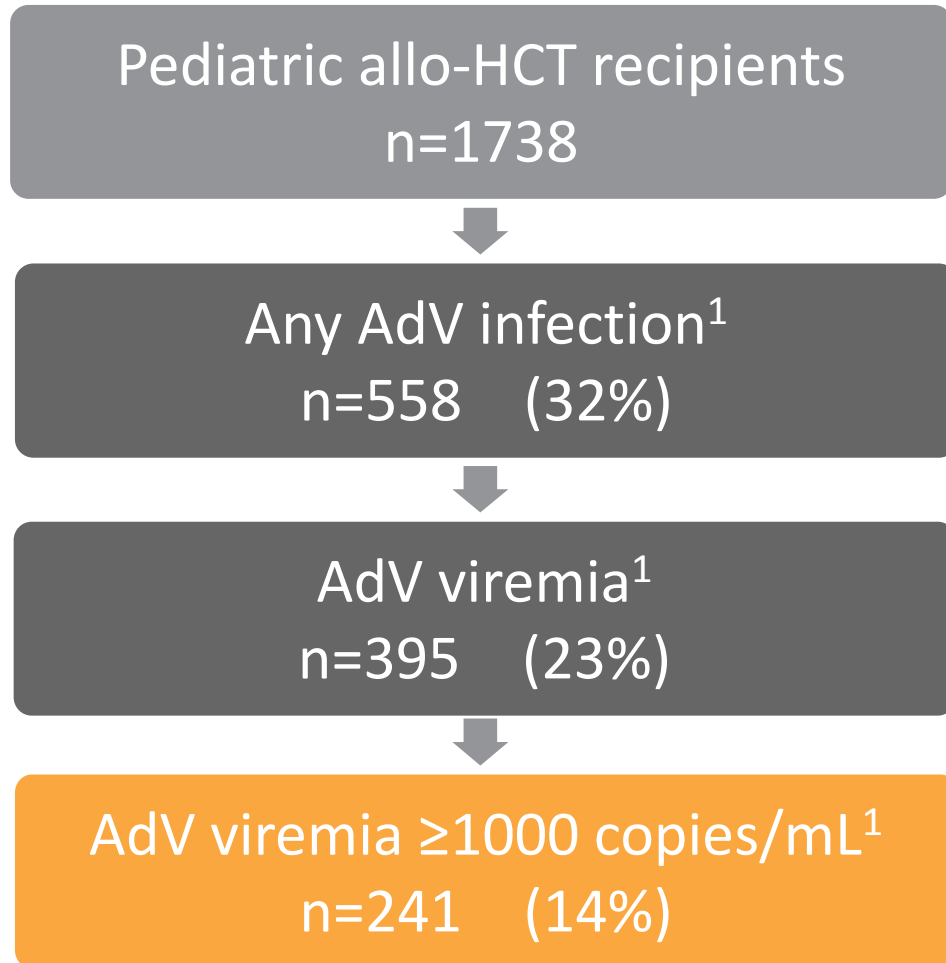
- Data were from transplants between January 2013 and September 2015 at participating centers
- Quantitative and qualitative data were extracted for AdV infection, AdV viremia, and AdV viremia ≥ 1000 copies/mL within 6 months of transplant
 - Results were stratified by age (pediatric [<18 years] vs adult)



Objectives of this analysis

- ⑥ To assess mortality within 6 months of AdV diagnosis in pediatric allo-HCT recipients with AdV viremia ≥ 1000 copies/mL
- ⑥ To investigate any correlation between viral burden and mortality (overall and non-relapse related)

Baseline characteristics in patients with AdV viremia ≥ 1000 copies/mL



¹Within 6 months of transplant

Demographic characteristics	Pediatric patients n=241
Age	
Median (range)	5.0 (0.1-17.0)
Sex	
Male	159 (66%)
Graft type	
BM	116 (48%)
PBSC	92 (38%)
Cord blood	33 (14%)

BM, bone marrow; PBSC, peripheral blood stem cell

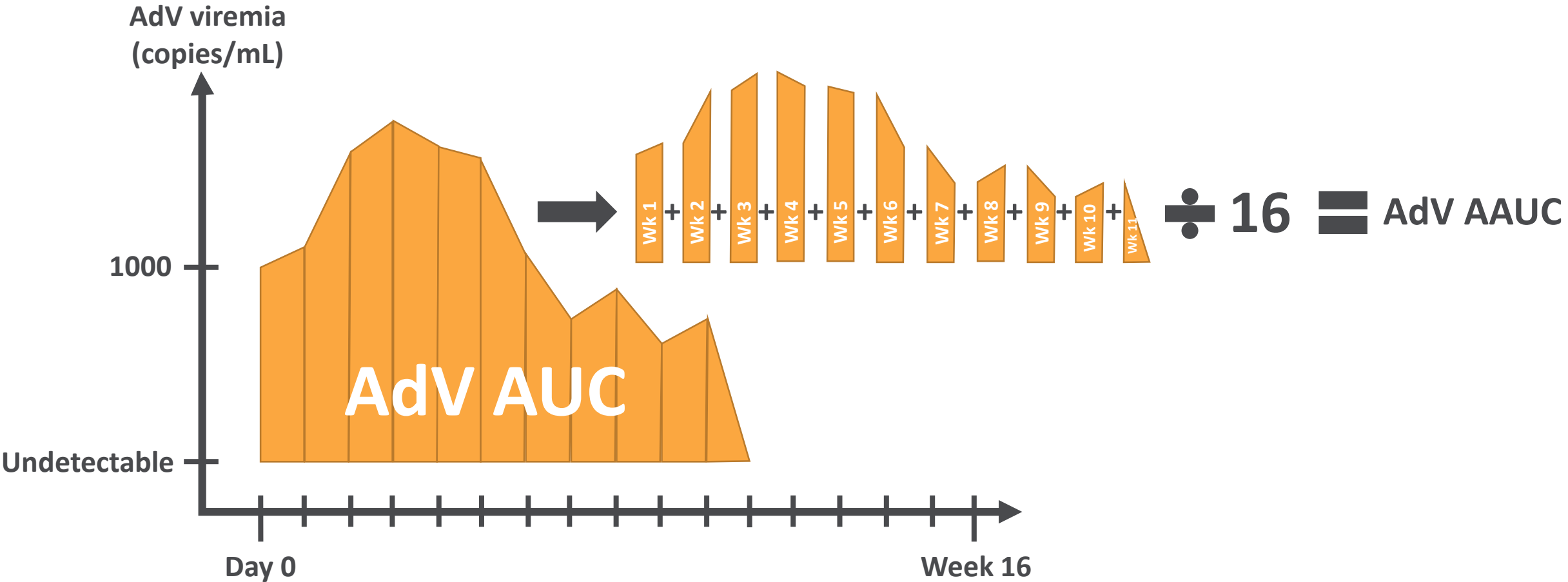
AdV AAUC as a potential surrogate for mortality

- ⦿ AdV viral burden was assessed as time-averaged area under the curve (AAUC) over 16 weeks from the time of viremia ≥ 1000 copies/mL
- ⦿ AdV AAUC is a virologic endpoint that quantifies the course and severity of disease in acute lytic viral infections such as AdV^{1,2}
- ⦿ AdV AAUC is a clinically relevant measure of viral burden that controls for variability in follow-up duration and has been used as a primary endpoint in Phase 2 and 3 studies of investigational antivirals³⁻⁵
- ⦿ We assessed the correlation between viral load measured by AdV AAUC and mortality in allo-HCT recipients

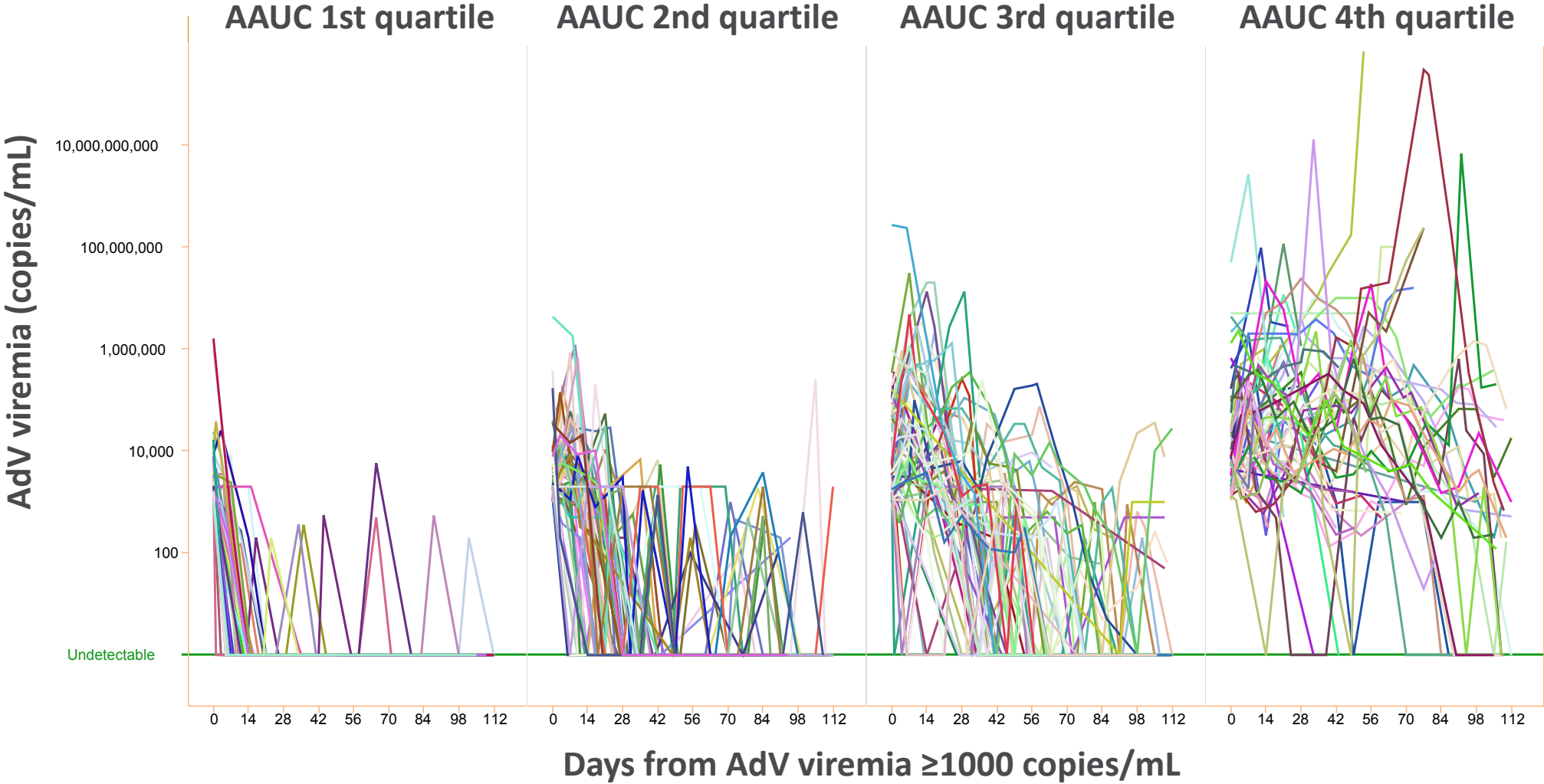
¹Vegvari C et al. *PLoS ONE*. 2016;11:e0158237. ²Heim A. *Expert Rev Anti Infect Ther*. 2011;9:943-5. ³DeVincenzo J et al. *N Engl J Med*. 2014;371:711-22.

⁴Lamarca A et al. *J Acquir Immune Defic Syndr*. 2006;4:598-606. ⁵Pulido F et al. *HIV Med*. 2004;5:296-302.

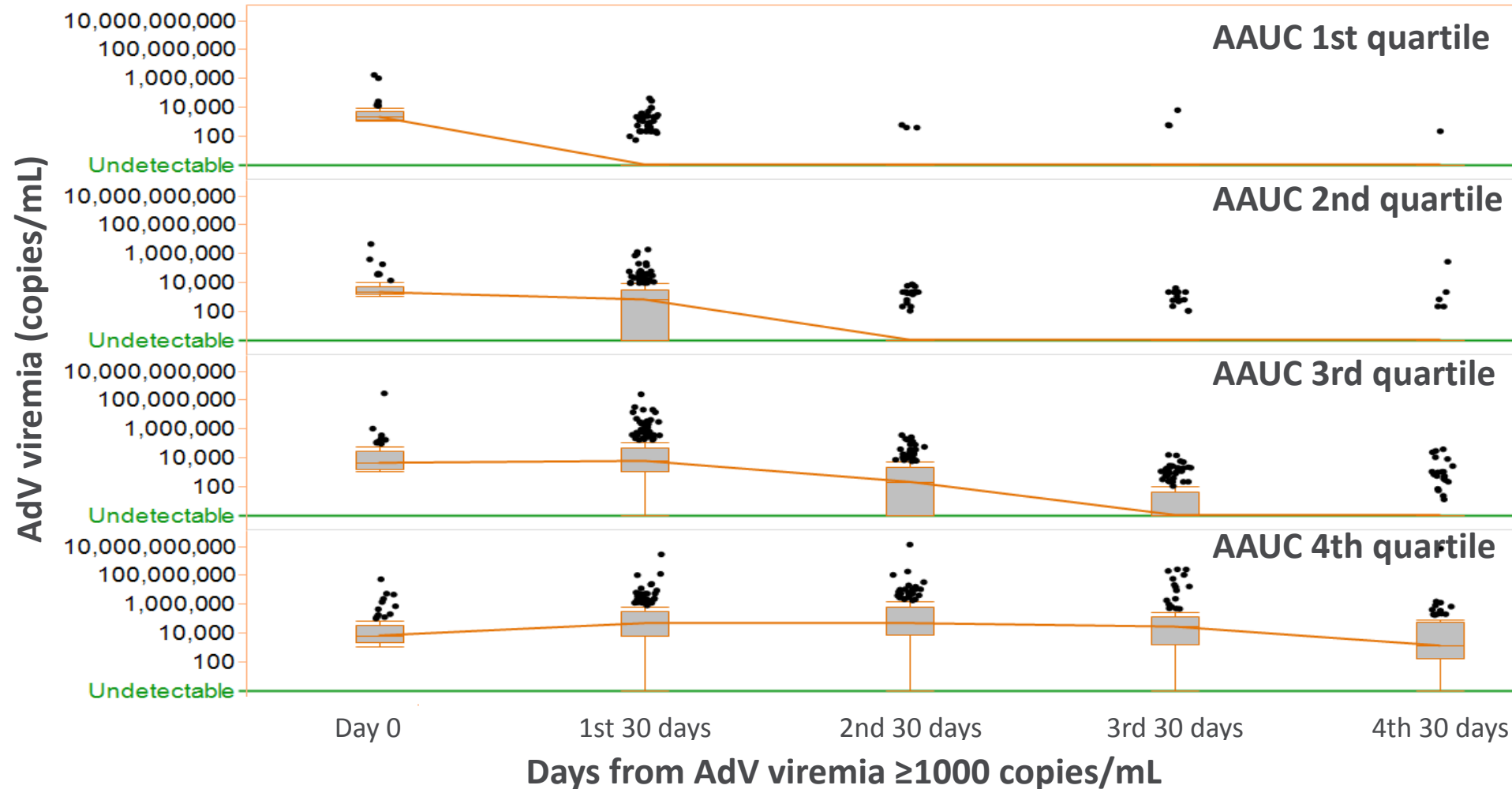
Calculating AdV average viral burden



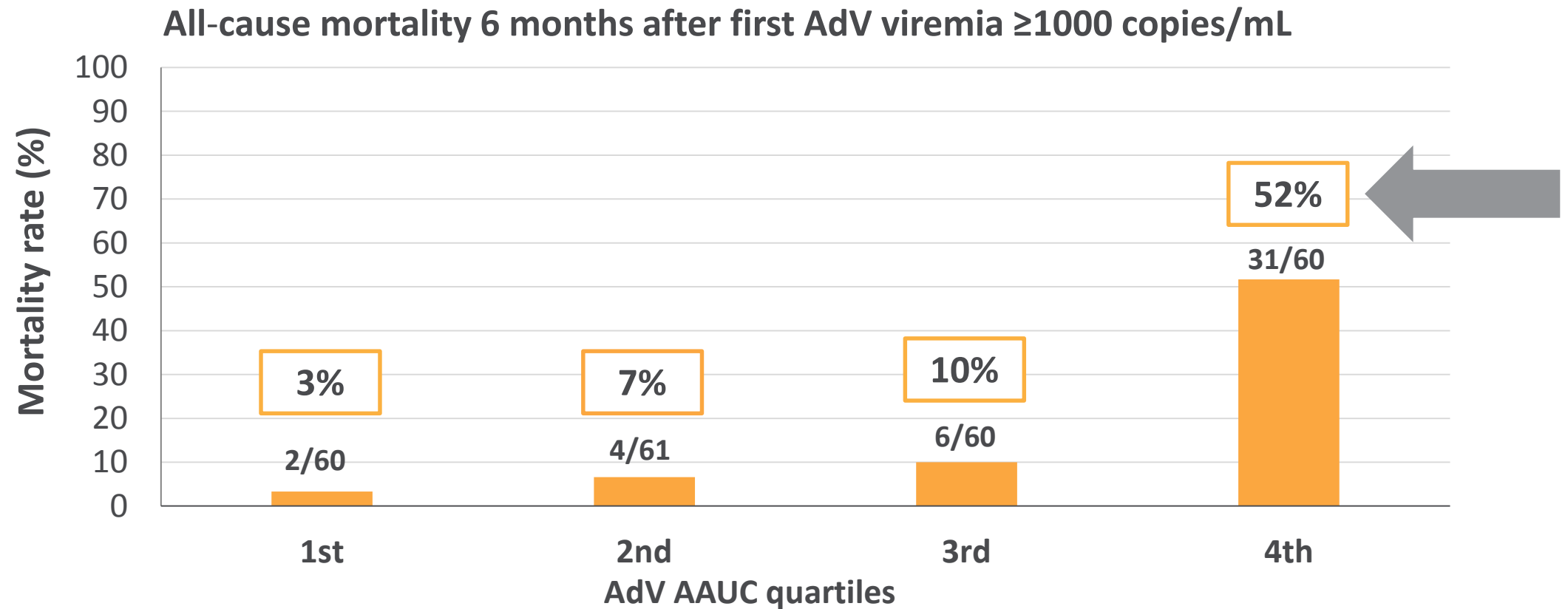
Peak and persistence of AdV viremia over time are higher in upper AdV AAUC quartiles



3rd & 4th quartiles reflect higher, more prolonged AdV viremia



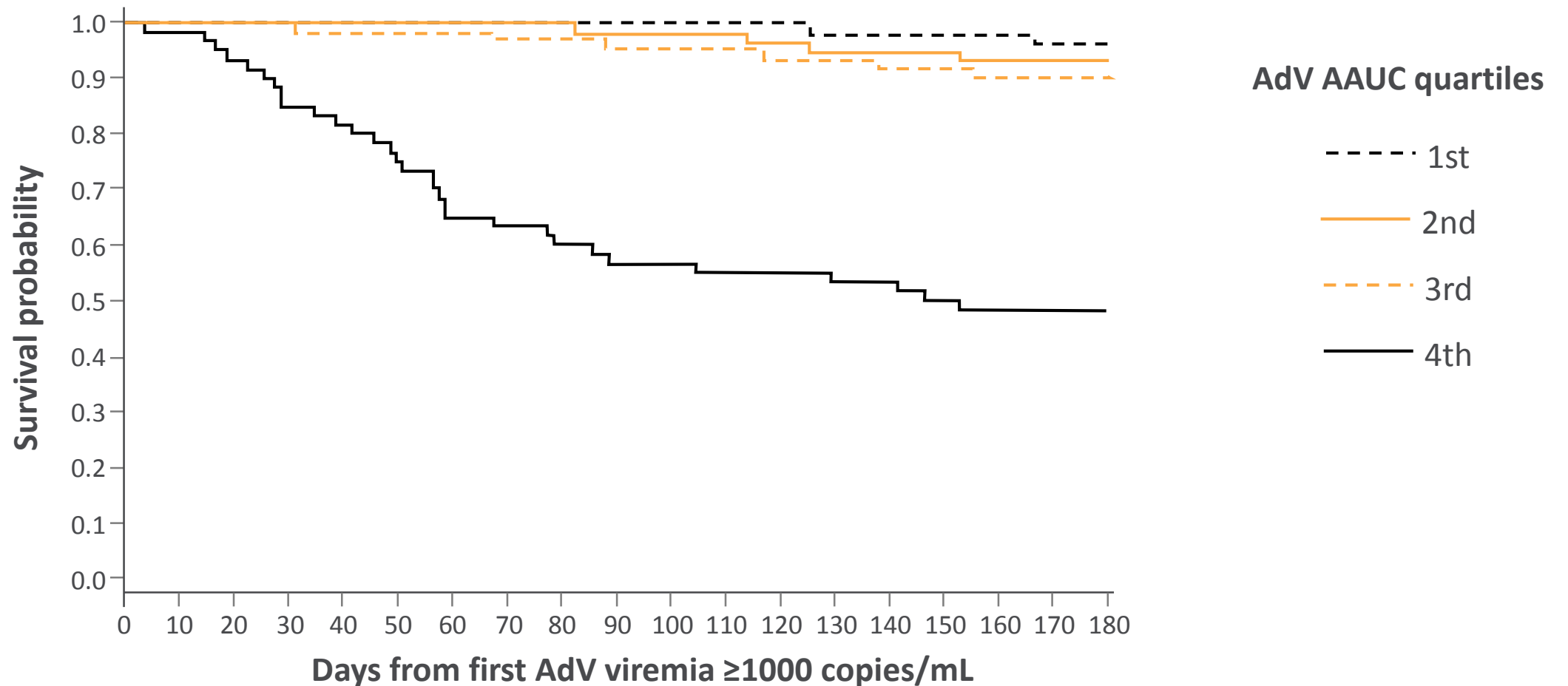
Increasing mortality was associated with AdV viral burden



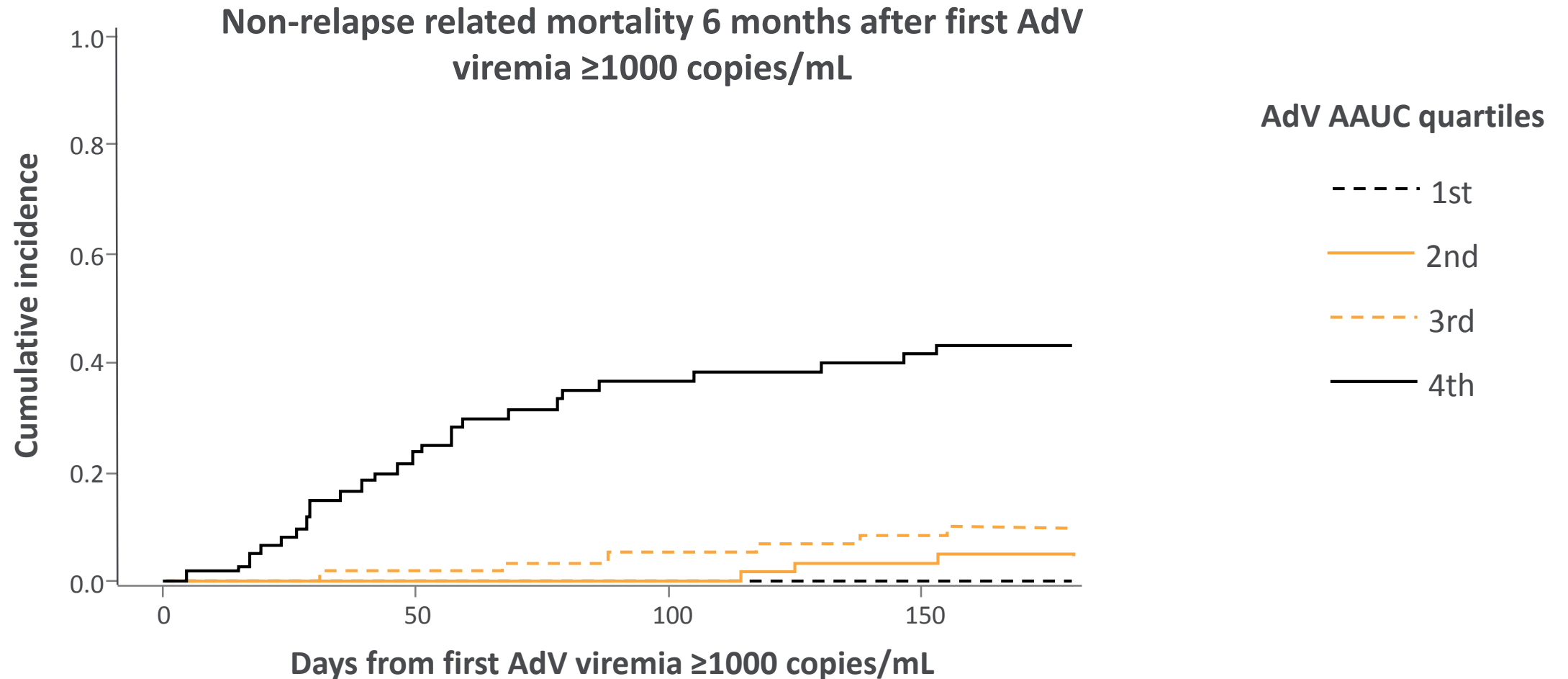
Comparable findings in non-relapse related mortality

40% of patients in the 4th quartile die within 2 months

All-cause mortality 6 months after first AdV viremia ≥ 1000 copies/mL

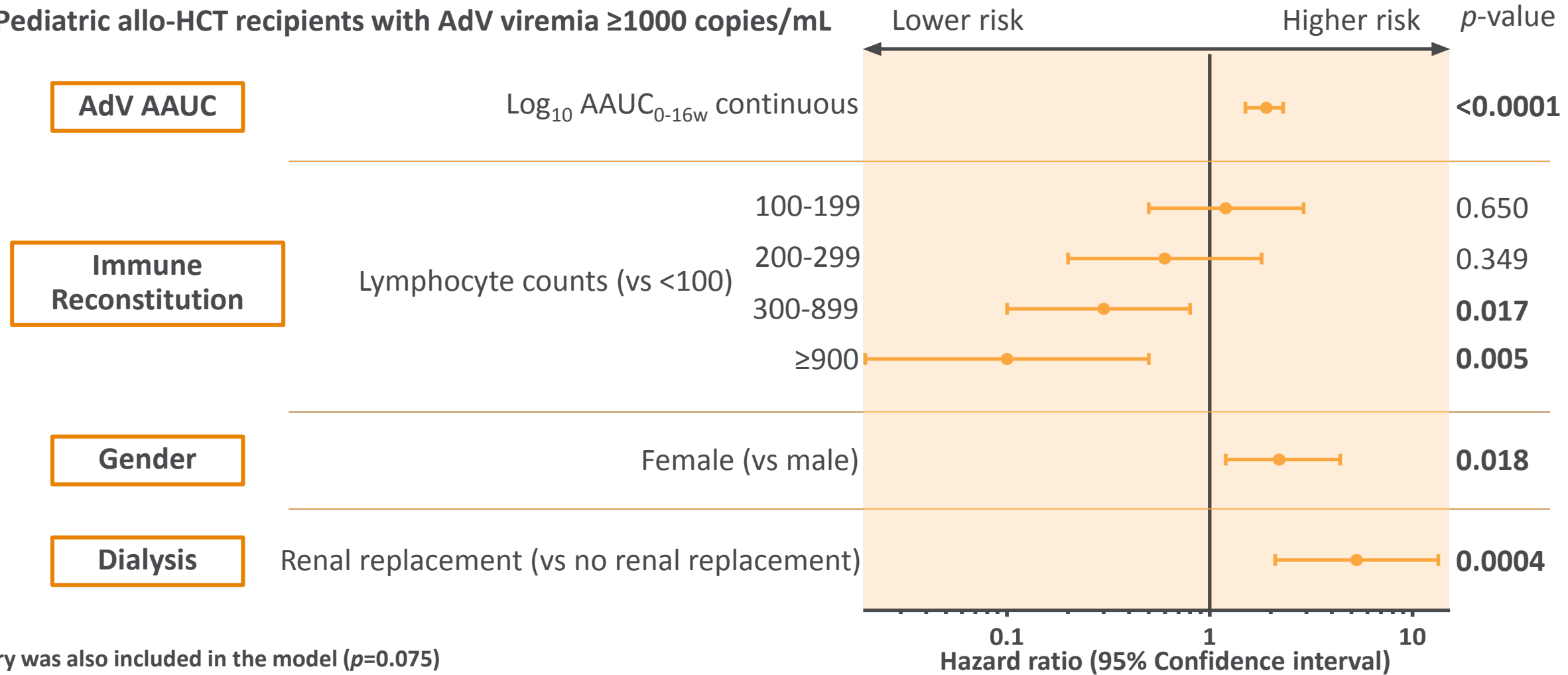


40% of patients in the 4th quartile die within 2 months



AdV viral burden and lymphocyte count significantly impact mortality risk

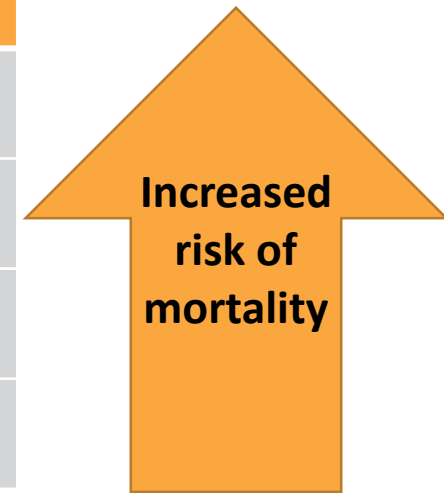
Pediatric allo-HCT recipients with AdV viremia ≥ 1000 copies/mL



AdV viral burden and lymphocyte count significantly impact mortality risk

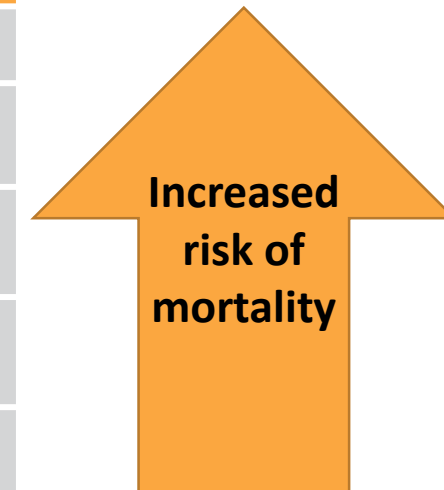
Higher AdV AAUC_{0-16weeks} increases the hazard of mortality

AdV AAUC _{0-16w}	HR [95% CI]
Median of 4th Quartile	11.7 [7.6-24.0]
Median of 3rd Quartile	2.7 [2.3-3.6]
Median of 2nd Quartile	1.5 [1.4-1.6]
Median of 1st Quartile	1.0 (ref)



Decreasing hazard of mortality with increasing lymphocyte count

Lymphocyte count	HR [95% CI]
<100	1.0
100-199	1.2 [0.5-2.9]
200-299	0.6 [0.2-1.8]
300-899	0.3 [0.1-0.8]
≥900	0.1 [0.0-0.5]



Conclusions

- Over half of the pediatric allo-HCT recipients who developed AdV viremia surpassed the threshold of ≥ 1000 copies/mL, shown to be associated with high levels of short-term mortality
- AdV AAUC was strongly correlated with both all-cause and non-relapse related mortality**
- AdV AAUC_{0-16weeks} and lymphocyte counts are independent prognostic survival factors
- AdV AAUC represents an appropriate measure of AdV viral burden to assess the potential benefits of antiviral therapies
- New treatment approaches that can decrease AdV viral burden may improve outcomes

The AdVance centers

FRANCE (10)

- Robert Debré Hospital, Paris
- CHU Angers
- Institut of Hematology, Lyon
- CHU Nancy
- CHU Montpellier
- CHU Bordeaux
- CHU Lyon
- CHU Nantes
- Saint Louis Hospital, Paris
- CHU Nice

SPAIN (12)

- Hospital Universitario y Politécnico La Fe (2)
- Hospital Universitario 12 de Octubre
- Hospital Universitario La Paz
- Hospital Universitario de Salamanca
- Hospital Universitario Vall d'Hebrón
- Hospital de la Santa Creu i Sant Pau (2)
- Hospital Universitario Reina Sofía
- Hospital Regional Universitario de Málaga
- Hospital Infantil Universitario Niño Jesús
- Hospital General Universitario Morales Meseguer

ITALY (9)

- Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Centro Trapianti Midollo Osseo, Milano
- Hospital Casa Sollievo Sofferenza, San Giovanni Rotondo
- Azienda Ospedale 'Riuniti e Morelli' Bianchi-Melacrino Centro Unico Regionale Trapianti Cellule Staminali e Terapia Cellulare, Reggio Calabria
- Pediatric Hematology/Oncology Department Policlinico San Matteo, Pavia

- Ospedale Civile Centro Trapianti Midollo Osseo Dip. Ematologia Medicina Trasfusionale e Biotecnologie, Pescara
- Pediatric Hematology/Oncology Department San Gerardo Hospital, Monza
- S.C. Oncoematologia Pediatrica e Centro Trapianti Regina Margherita, Torino
- Oncoematologia e TMO, Ospedale 'La Maddalena' Palermo
- Ospedale Bambin Gesù-Dip. Oncoematologia Pediatrica e Medicina Transfusionale, Roma



GERMANY (7)

- Charité Campus Virchow Klinikum
- J. W. Goethe Universität
- Medizinische Hochschule Hannover
- Universitätsklinikum Jena
- Universitätsklinikum Köln
- Universitätsklinik Tübingen
- Klinikum der Universität München (LMU)

UK (10)

- Royal Manchester Children's Hospital
- Bristol Royal Children's Hospital
- Sheffield Children's Hospital
- St. James's University Hospital and The General Infirmary, Leeds
- Great North Children's Hospital, Newcastle
- Great Ormond Street Hospital, London
- University College London Hospitals,
- University Hospital of Wales Cardiff
- The Royal Marsden Hospital, London
- Birmingham Children's Hospital

The NETHERLANDS (1)

- UMC Utrecht

CZECH REPUBLIC (1)

- Hospital Motol, Praha