Summary

What is your main question?

- Which characteristics at ART initiation predict treatment failure in children starting first-line ART (including dolutegravir (DTG))?

What did you find?

- Younger age, lower BMI-for-age and lower CD4% at ART initiation predicted higher risk of treatment failure

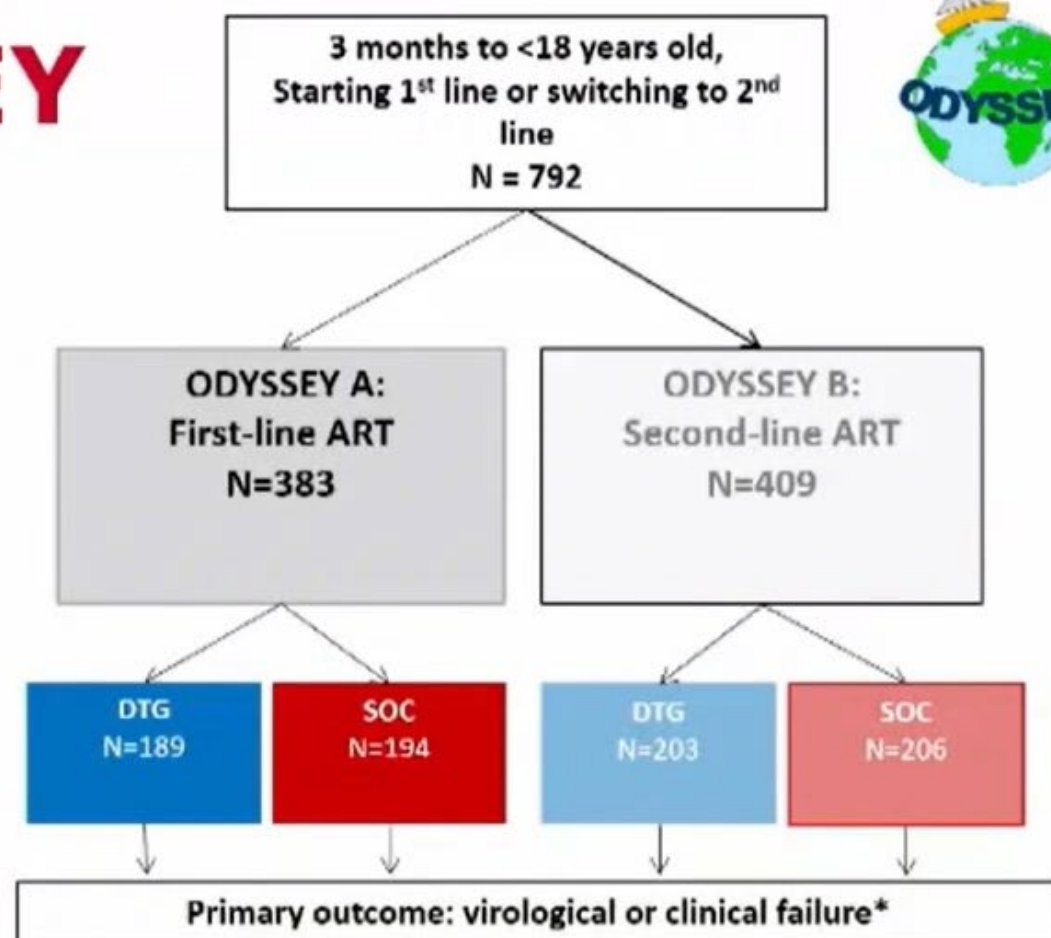- Other predictors included an ongoing WHO stage 3/4 event and higher neutrophils

Why is it important?

- Informs targeted support for children at highest risk of treatment failure

The ODYSSEY Trial

- Evaluated efficacy and safety of DTG-based ART vs. standard of care (SOC) in children starting first- or second-line treatment

- Two weight cohorts (≥14 kg and <14 kg)

- Primary outcome was treatment failure (clinical or virological) by 96 weeks
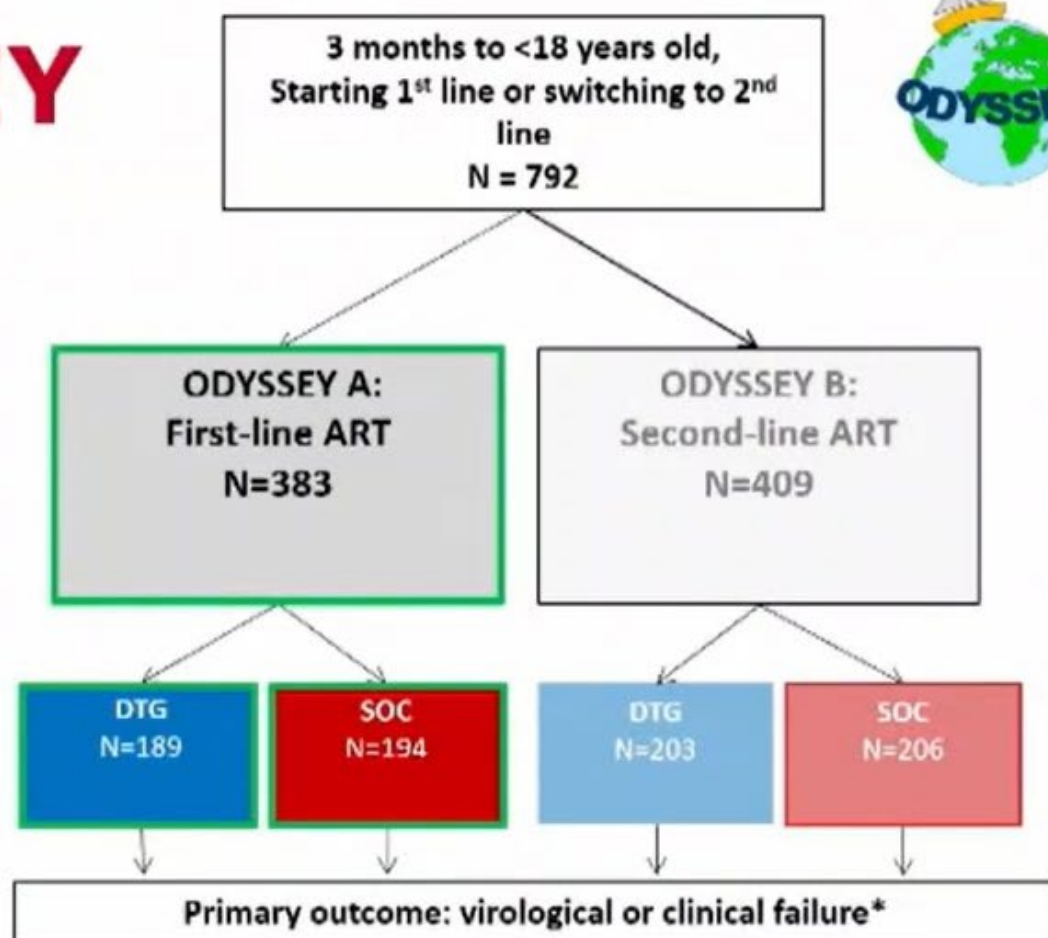
- DTG showed superior efficacy in both weight cohorts

3 months to <18 years old, Starting 1st line or switching to 2nd line
N = 792

ODYSSEY A: First-line ART N=383

ODYSSEY B: Second-line ART N=409

DTG N=189

SOC N=194

DTG N=203

SOC N=206

Primary outcome: virological or clinical failure*

*(1) a decrease of less than 1 log10 in viral load by week 24, or a viral load of >50 copies per ml at week 24 if the baseline viral load was <500 copies per ml, accompanied by a switch in ART for treatment failure; (2) virologic failure, defined as two consecutive viral load measurements of ≥400 copies per mL, with the first measurement occurring at or after week 36; (3) a new or recurrent acquired immunodeficiency syndrome (AIDS) defining event (WHO stage 4) or severe WHO stage 3 event; or (4) death from any cause.

Population

Characteristics at ART initiation

- 381 children: 309 ≥14kg, 72 <14kg
- Age, median [IQR]: 10.5 years [6.5 to 14.0]
- CD4%, median [IQR]: 20% [12 to 28]
- BMI-for-age z-score, median [IQR]: -0.58 [-1.48 to +0.25]
- 73 (19%) had an ongoing WHO stage 3/4 event at ART initiation (40 tuberculosis).
- SOC: ≥14kg, 92% EFV; <14kg, 78% LPV/r

Treatment failure by 96 weeks

- 75 (20%) children: 58 (77%) virological, 17 (23%) clinical.
- 24 on DTG, 51 on SOC.

Germany
Spain, UK
Portugal
18 (5%)

Thailand
50 (13%)

Uganda
131 (34%)

Zimbabwe
86 (23%)

Africa
313 (82%)

South Africa
96 (25%)

*two participants from the SOC arm dropped due to having zero follow-up post randomisation

Methods

- Predictors were assessed using Cox regression models

- All models were adjusted for trial arm (DTG vs SOC) and age*

- First-degree fractional polynomials were considered for continuous variables

- Domain-specific models (e.g. anthropometrics) were selected ($p<0.2$ for retention).

- Full joint model selected from domain-specific predictors ($p<0.1$ for retention)

- Bootstrap resampling was used to assess robustness of models

*Results in abstract are based on models adjusted for trial arm and weight

Predictors at ART initiation by domain

Trial arm and age included a-priori

Anthropometrics: weight, middle-upper arm circumference, height-for-age and **BMI-for-age**

HIV markers: CD4/CD8 ratio, **CD4%***, viral load and **ongoing WHO stage 3/4 event**

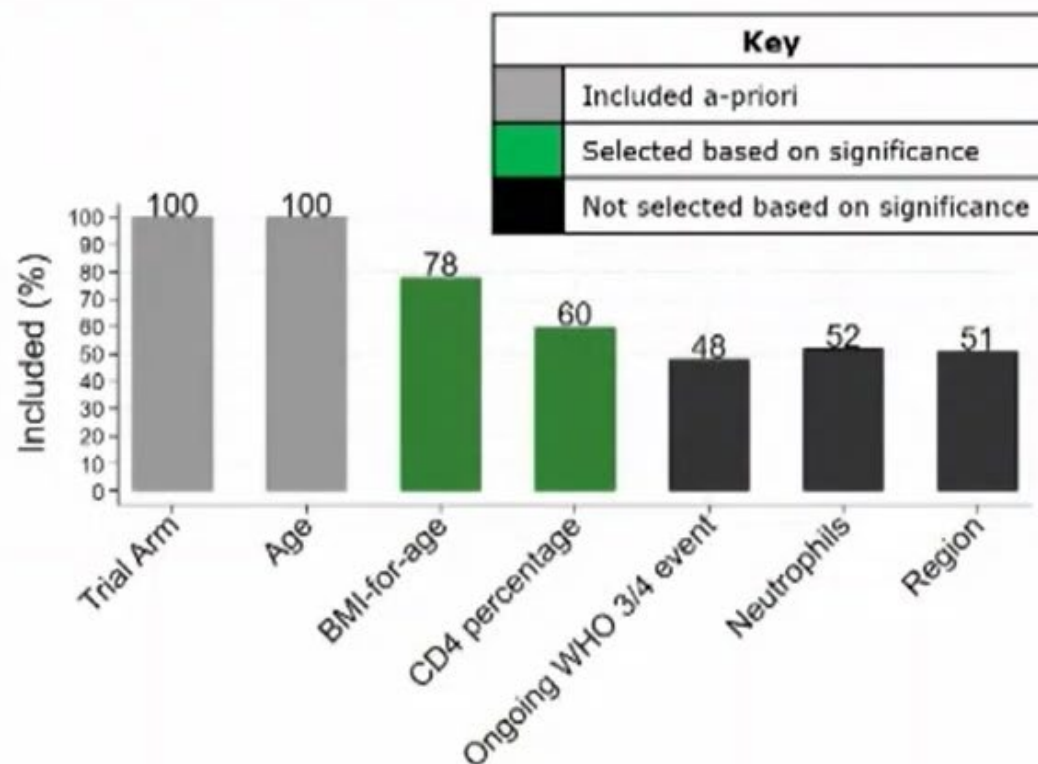*Haematology*: platelets, **neutrophils** and haemoglobin

Demographics: sex, primary caregiver and **region**

*CD4 results were expressed as percentages of total lymphocyte counts, as these are less variable with age

Predictors of Treatment Failure

Full model adjusted for trial arm and age

Factor	HR	95% CI	p-value
Trial arm (DTG vs. SOC)	0.47	(0.29-0.76)	0.002
Age (per year)	0.91	(0.87-0.95)	<0.001
BMI-for-age (per unit Z-score)	0.77	(0.66-0.90)	0.001
CD4 percentage (per 1%)	0.98	(0.96-1.00)	0.048
Ongoing WHO 3/4 event (Yes)	Dropped		0.20
Neutrophils (per 10⁹/L)	Dropped		0.16
Region (African site vs. other)	Dropped		0.13

Bootstrapping variable selection

Key
- Included a-priori
- Selected based on significance
- Not selected based on significance

Bar chart (Included %): Trial Arm 100, Age 100, BMI-for-age 78, CD4 percentage 60, Ongoing WHO 3/4 event 48, Neutrophils 52, Region 51

➢ **No differences by trial arm**

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Trial Arm and Age

Treatment failure by trial arm[1] (DTG/SOC)

Trial Arm	96 weeks
DTG	0.10 (0.02-0.19)
SOC	0.21 (0.07-0.35)

— DTG
--- SOC

Failure Probability (y-axis: 0.00, 0.20, 0.40, 0.60, 0.80, 1.00)

Weeks since ART initiation (x-axis: 0, 12, 24, 36, 48, 60, 72, 84, 96)
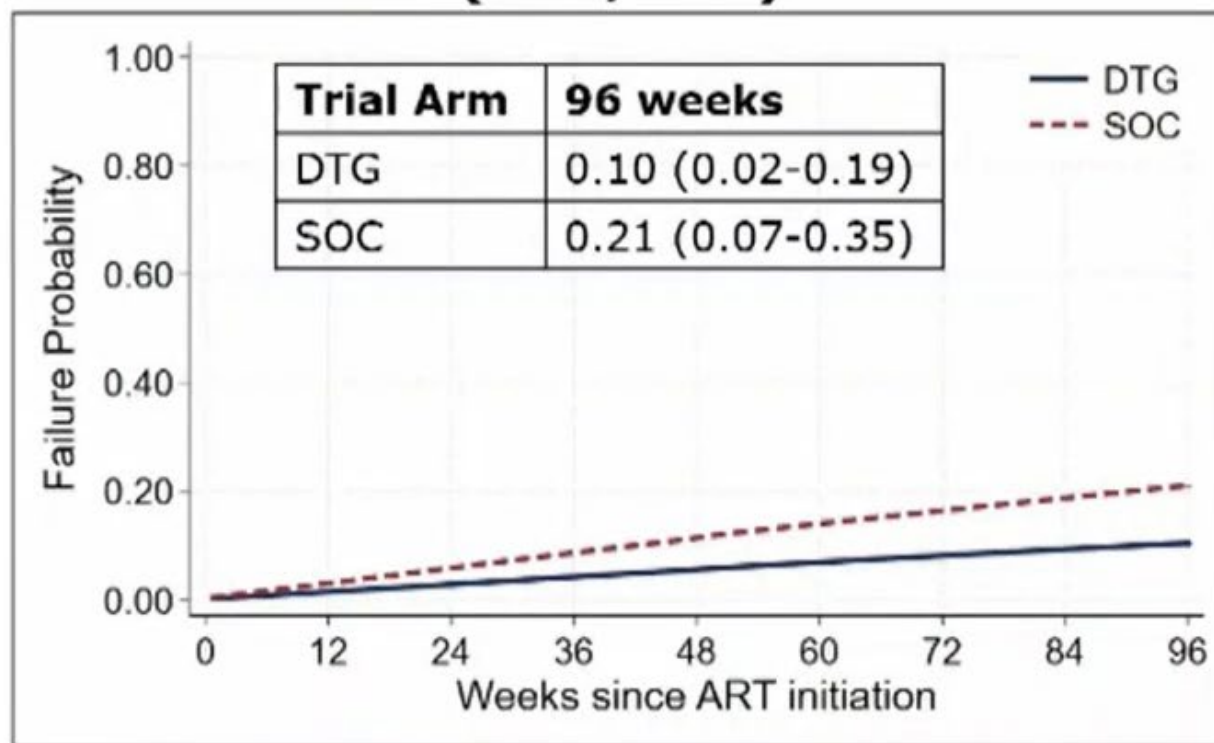
[1]Using median age (10.5yrs), CD4% (20%), BMI-for-age (-0.58)

Treatment failure by age at ART initiation[2] (DTG arm)

Age (Yr)	96 weeks
1	0.23 (0.09-0.37)
2	0.21 (0.08-0.35)
6	0.15 (0.04-0.26)
12	0.09 (0.01-0.17)

······ 1 year old
--- 2 year old
— — 6 year old
—— 12 year old

Failure Probability (y-axis: 0.00, 0.20, 0.40, 0.60, 0.80, 1.00)

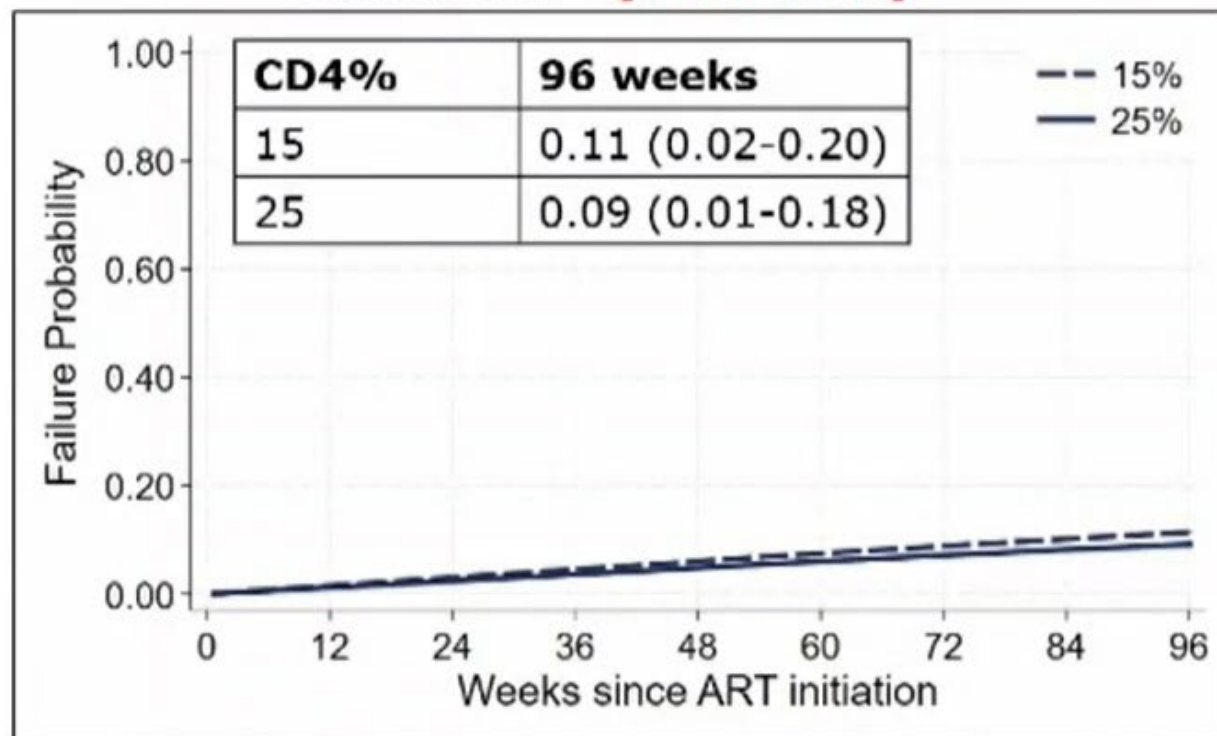Weeks since ART initiation (x-axis: 0, 12, 24, 36, 48, 60, 72, 84, 96)
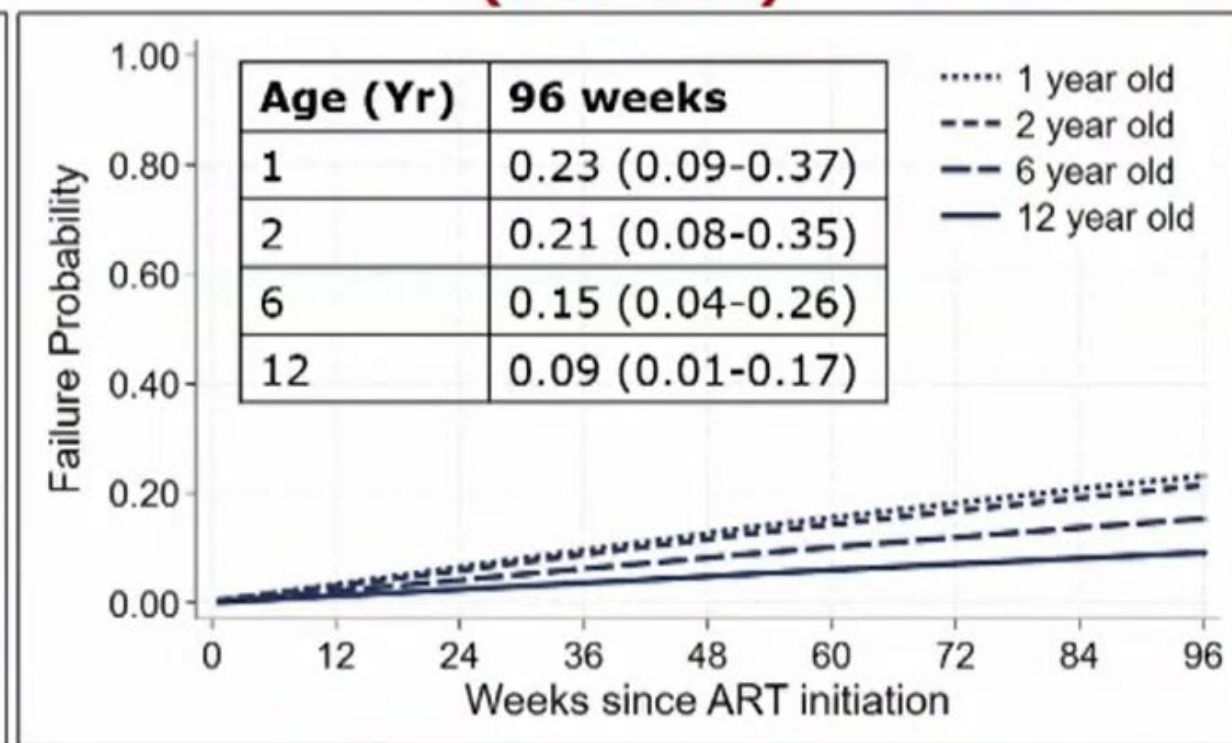
[2]Using median CD4% (20%) and BMI-for-age (-0.58)

CD4% and BMI-for-age

Treatment failure by CD4% at ART initiation[1] (DTG arm)

CD4%	96 weeks
15	0.11 (0.02-0.20)
25	0.09 (0.01-0.18)

Legend: -- - 15% — 25%

[1]Using the median age (10.5) and BMI-for-age (-0.58)

Treatment failure by BMI-for-age Z-score at ART initiation[2] (DTG arm)

BMI-for-age Z-score	96 weeks
-3	0.19 (0.00-0.37)
-1.5	0.13 (0.01-0.25)
0	0.09 (0.02-0.16)
1	0.07 (0.01-0.13)

Legend: ······ -3 --- -1.5 -- - 0 — 1
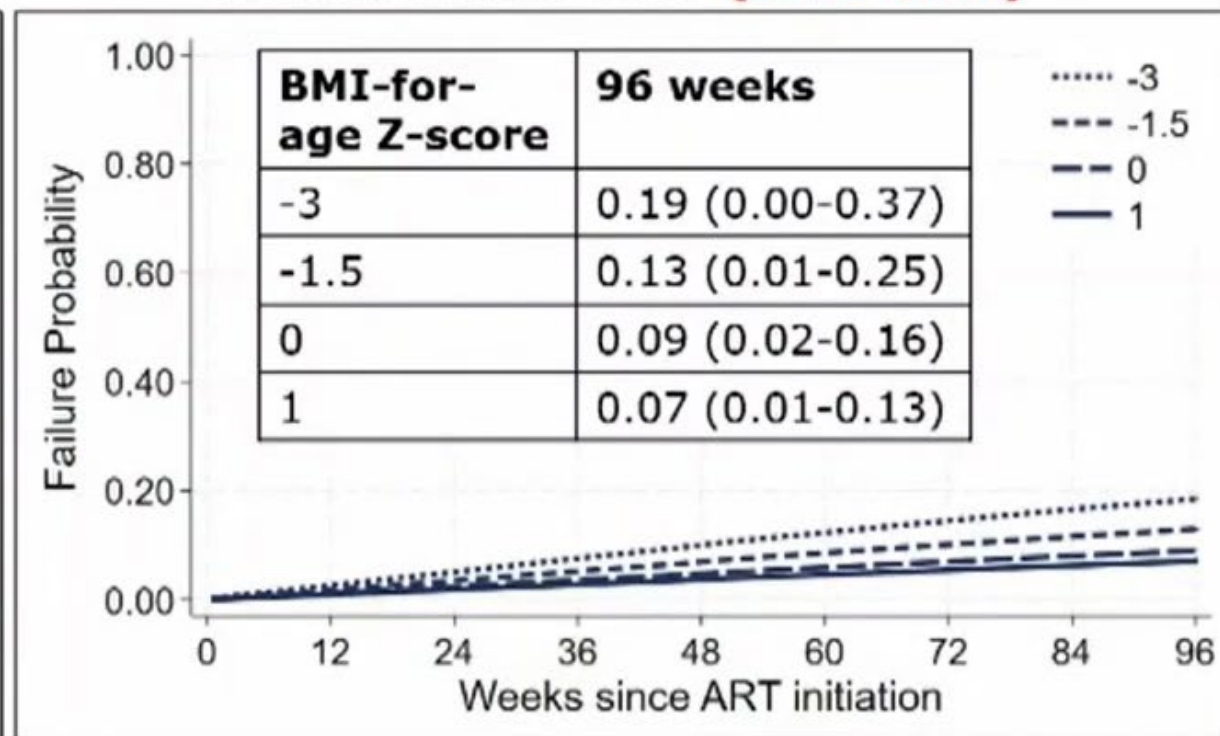
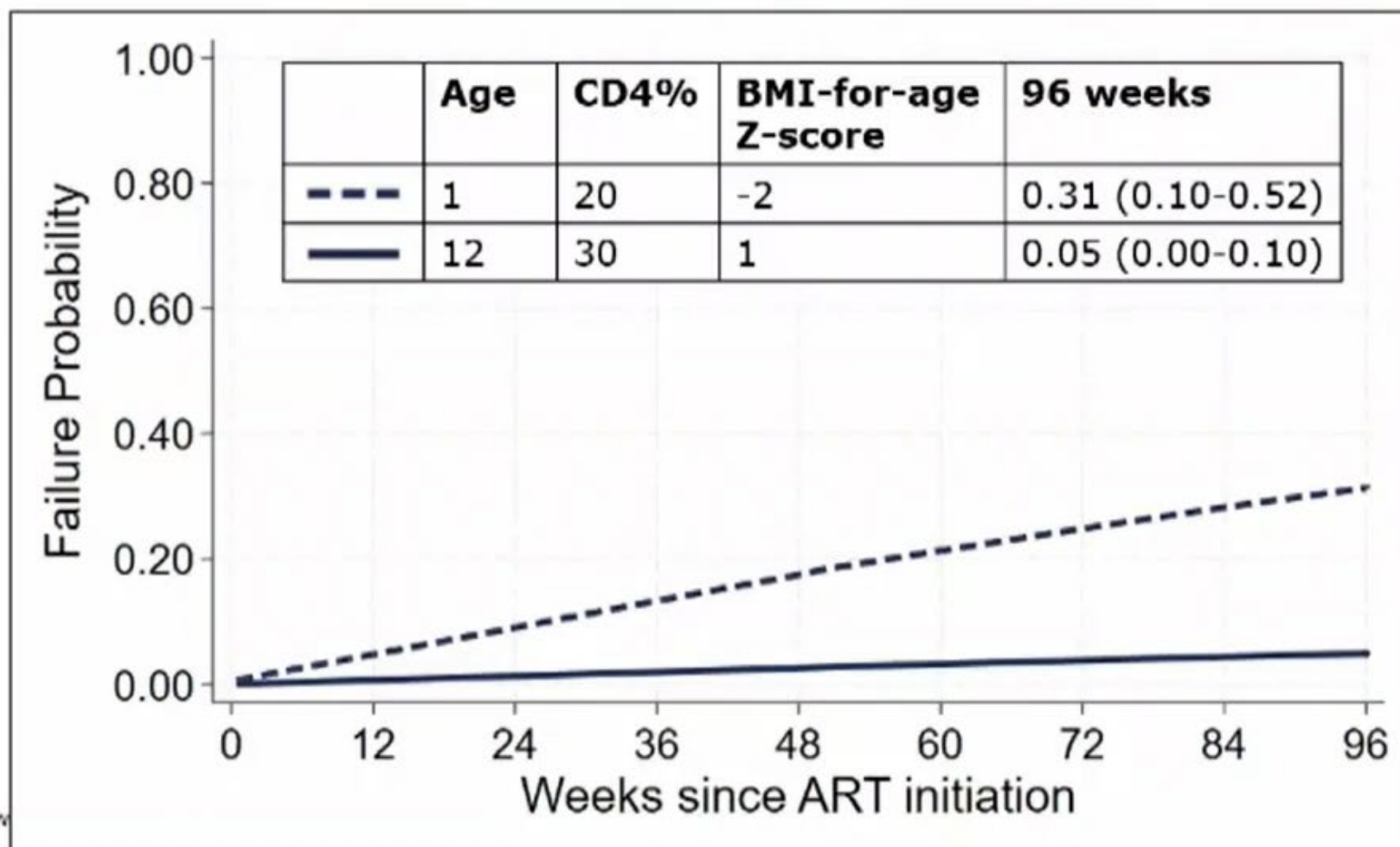[2]Using the median age (10.5) and CD4% (20%)

High risk vs. low risk of treatment failure by characteristics at ART initiation (DTG arm)

Alternative virological failure definition

- Composite primary endpoint including virological and clinical failure

- Most virological failures (97%) were 2 VL $\geq$400 c/mL after 36 weeks

- 47/56 (84%) had 2 VL $\geq$1000 c/mL by week 96

- Predictors using the higher threshold ($\geq$1000 c/mL) were the same, but also included an ongoing WHO stage 3/4 event

Summary

- Children receiving DTG-based ART had a significantly lower risk of treatment failure compared to those on SOC

- Other predictors of treatment failure were the same on DTG and SOC

- Predictors include younger age, lower BMI-for-age, lower CD4%, ongoing WHO stage 3/4 event and higher neutrophils

- Findings could help clinicians identify children at higher risk of early treatment failure and provide the basis for an online tool

- Future research should evaluate interventions (e.g. non-oral ART, enhanced treatment, adherence support) for high-risk children

Thank you

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- Data Monitoring Committee
- Endpoint Review Committee
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