

**DTG/3TC is non-inferior  
to DTG-based 3-drug ART in children with HIV:  
D3/Penta 21 week 96 results**

**Anna Turkova** on behalf of the D3/Penta 21 trial team

MRC Clinical Trials Unit at UCL, Institute of Clinical trials and Methodology, London, United Kingdom

Financial disclosure: Chief Investigator of the D3/Penta 21 trial, funded by ViiV Healthcare

# Background

---

**Two-drug ART regimens (2DR) are emerging alternatives to standard three-drug regimens (3DR).**

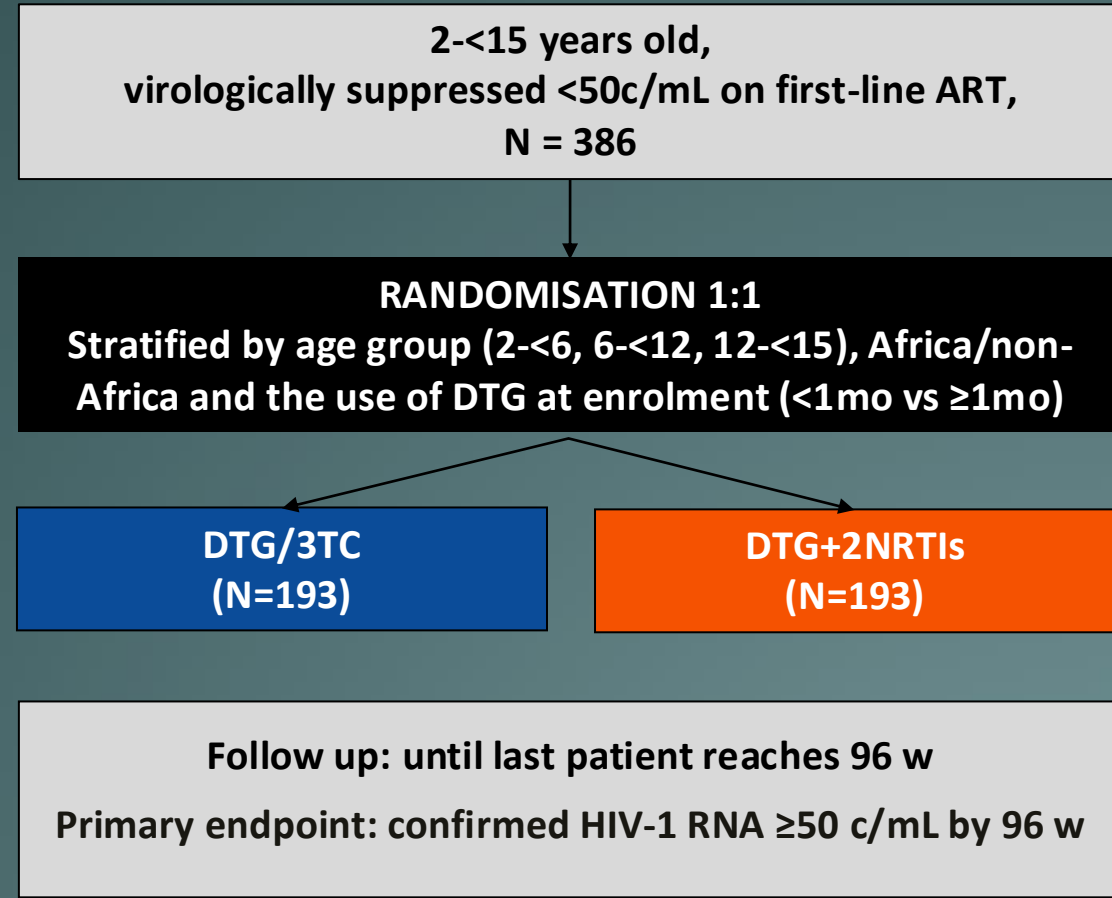
**DTG/3TC is most widely used oral 2DR in adults, with excellent efficacy, safety, and reassuring resistance data.**

**Data in children are limited.**

# D3 / Penta 21



- Open-label randomised (1:1) multi-centre 96w non-inferiority trial comparing **DTG/3TC** & **DTG+2NRTIs (DTG-3DR)**\*
- Children aged 2 to <15 years,  $\geq 10$ kg, virologically suppressed for  $\geq 6$  months, with no previous treatment failure
- **Primary endpoint:** confirmed HIV-1 RNA viral load (VL)  $\geq 50$  c/mL by 96-weeks
- Employed a ‘smooth away from expected’ (SAFE) non-inferiority frontier: NI margin and significance level dependent on the event rate in the DTG-3DR arm\*\*
- Visits were 12 weekly, real-time VLs at 24w, 48w & 96w , additional VLs as per country guidelines; retrospective VLs at other visits
- Children <20kg had dispersible tablets (DT), 20 to <25kg had either DT or adult film-coated tablet (FCT),  $\geq 25$ kg FCT
- Intensive PK study nested for regulatory submission\*\*\*



The trial sponsored by Penta, funded by ViiV Healthcare

# Baseline characteristics



**386 children enrolled: 193 DTG/3TC, 193 DTG-3DR**

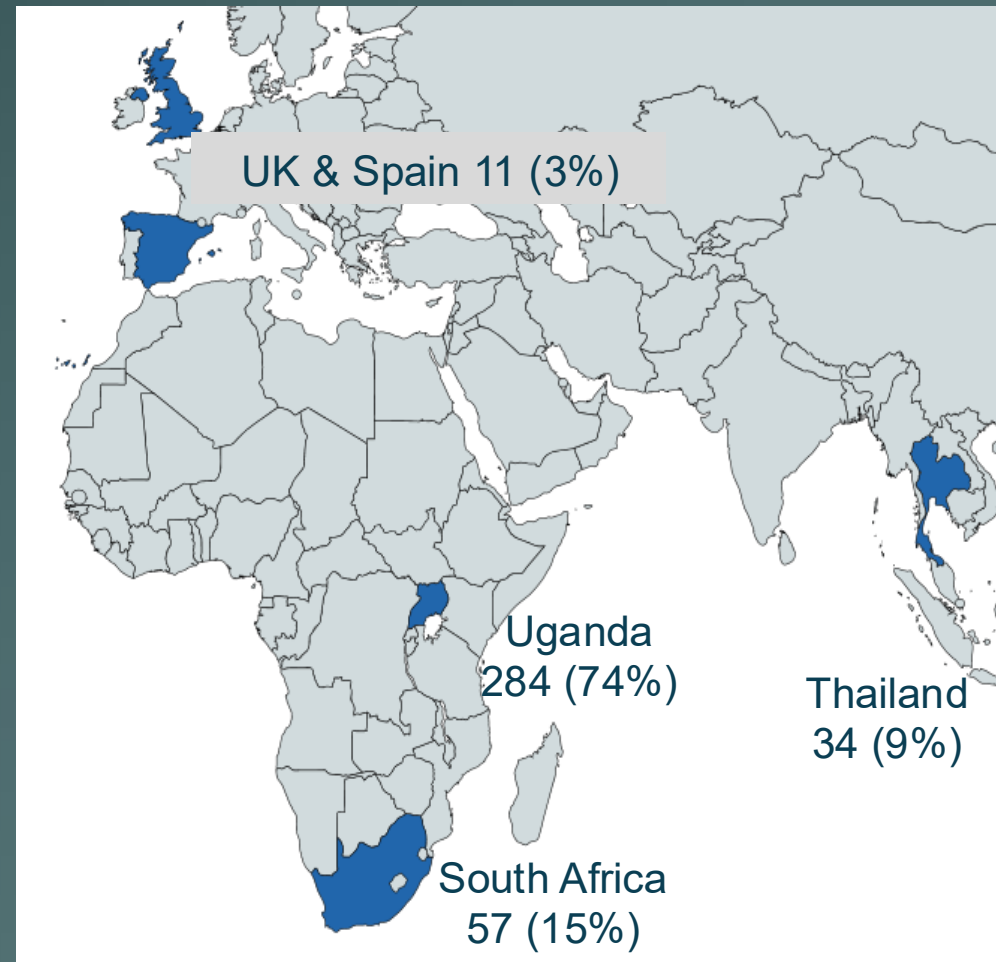
## Median:

- **Age:** 8.3years (IQR 5.5, 12.0, range 2.2-15)
- **Weight:** 23Kg (IQR 18-33)
- **Sex:** 54% female
- **CD4%:** 38% (IQR 33-43)

**326 (84%)** were on DTG  $\geq$ 1month at study entry

**In DTG-3DR, 152 (79%) ABC/3TC and 36 (19%) TDF/3TC; 5 other**

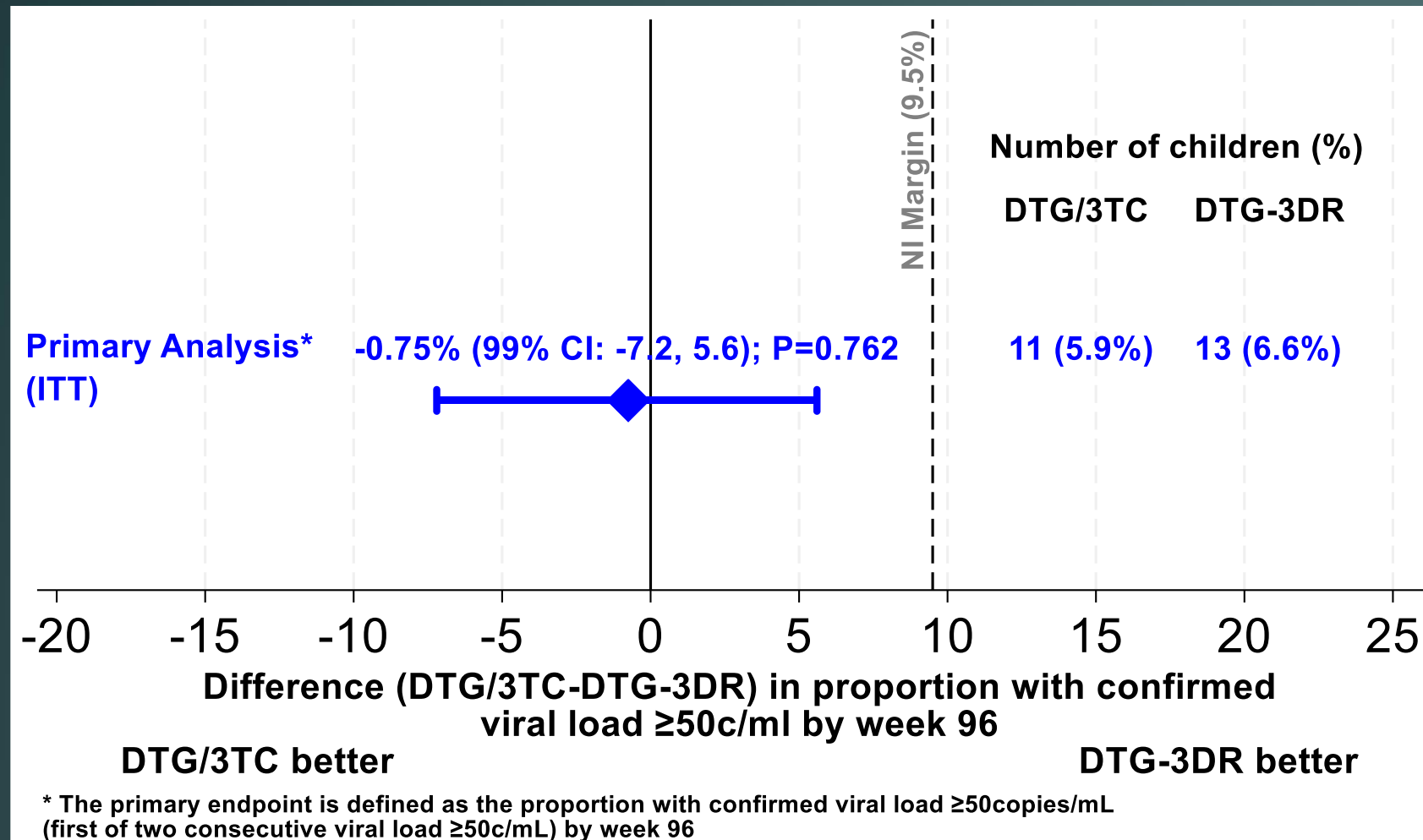
Baseline characteristics were well balanced by arm



# Primary outcome: ITT results



## Non-inferiority of DTG/3TC vs DTG-3DR demonstrated

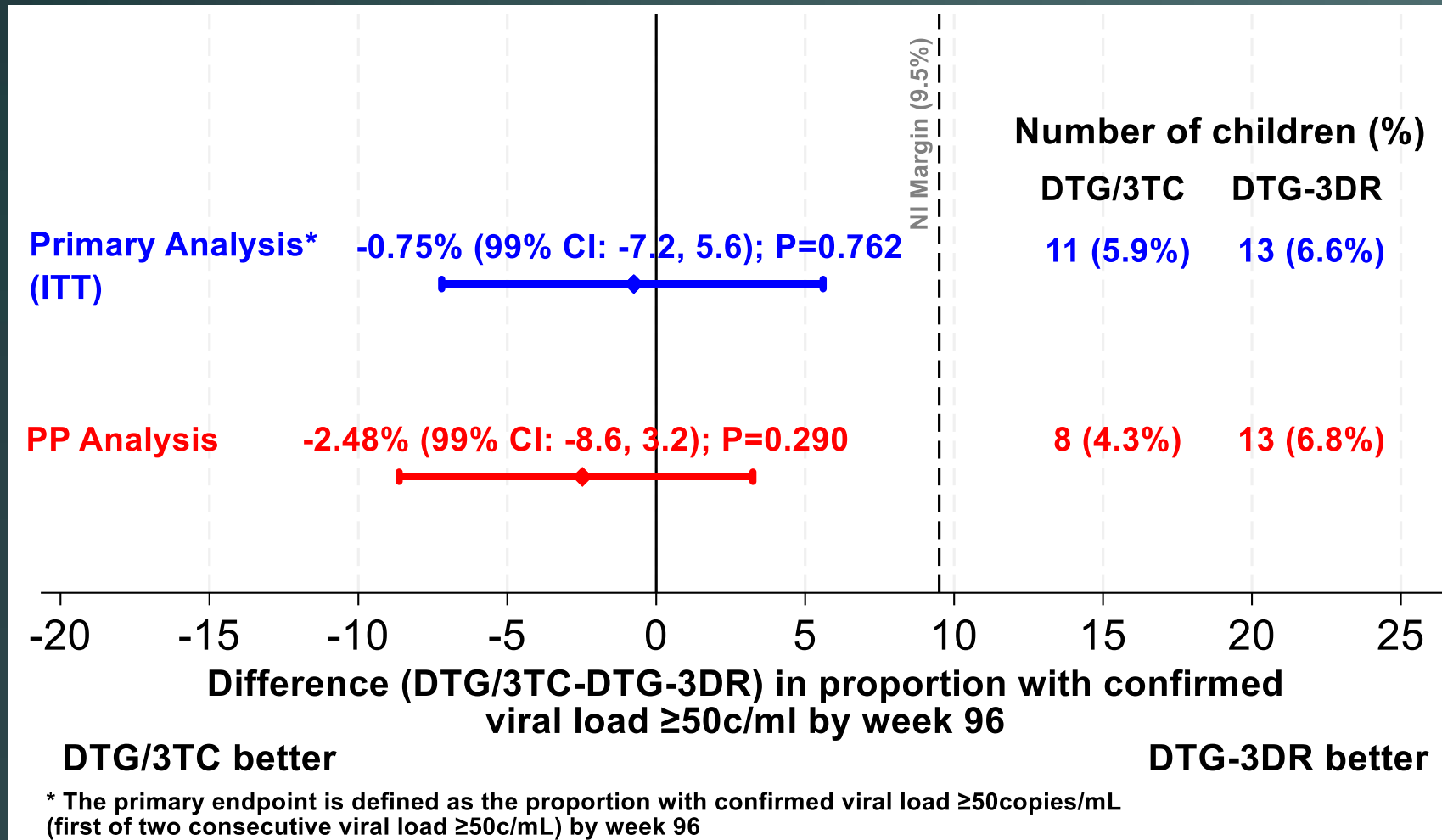


- Based on SAFE NI frontier: 9.5% NI margin and 99% CI

# Primary outcome: ITT & per-protocol results



## Non-inferiority of DTG/3TC vs DTG-3DR demonstrated

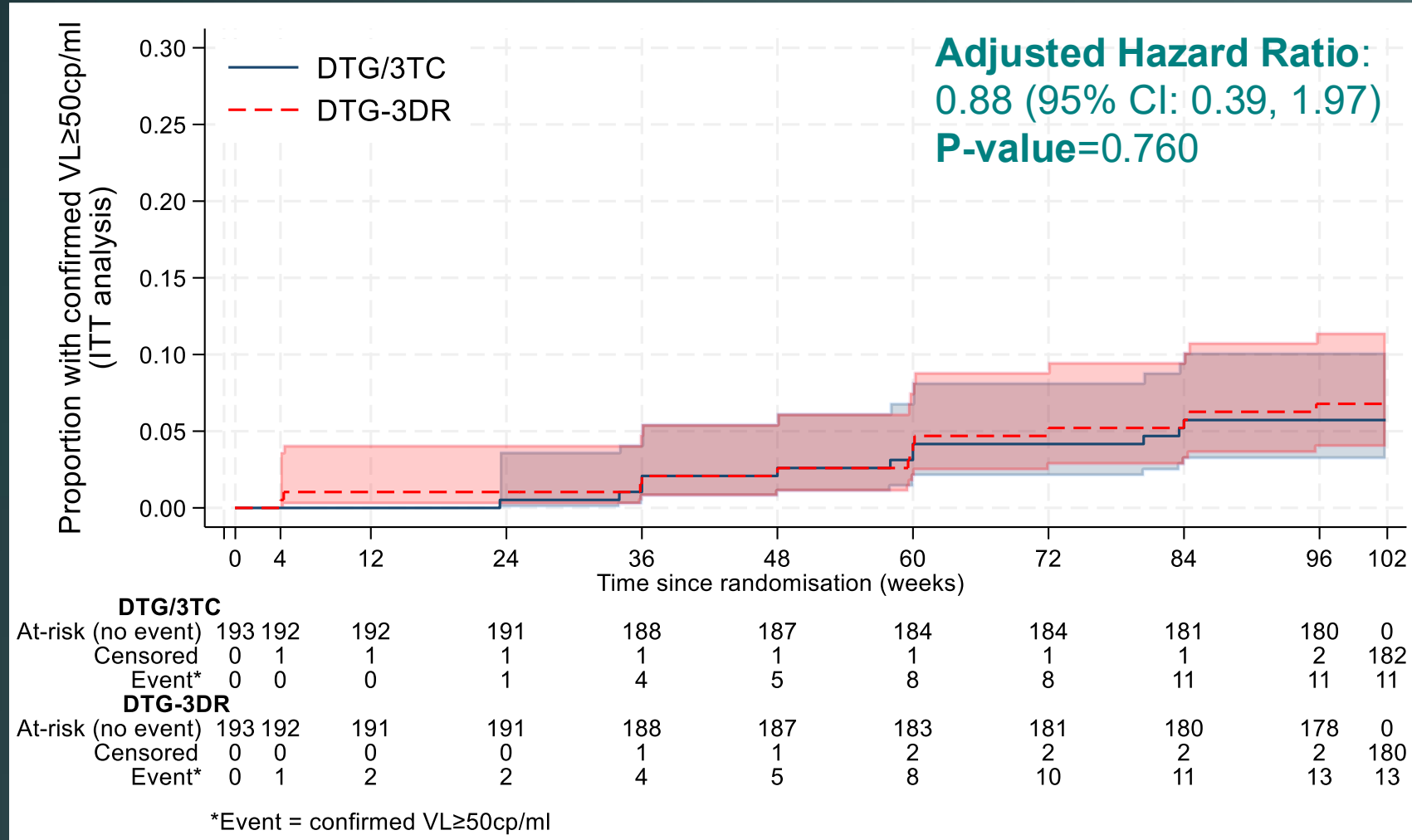


- Based on SAFE NI frontier: 9.5% NI margin and 99% CI

# Kaplan-Meier estimates for confirmed VL $\geq 50$ cp/ml by 96w



## No difference in time to confirmed VL $\geq 50$ cp/mL between arms



No heterogeneity in treatment effect by baseline age, region or DTG at enrolment

## Few children had ART changes

### ART switches:

- **7 (4%)** participants in **DTG/3TC** switched to 3-drug regimens (6 who met primary endpoint\* and 1 during pregnancy); 6/7 remained on DTG
- **14 (7%)** participants in **DTG-3DR** had ART changes (1 changed to BIC/TAF/FTC for simplification, 13 remained on DTG and had NRTI change for simplification/growth/other)

\* The other 5/11 in DTG/3TC who met primary endpoint did so due to the use of retrospective VL; of these, 3 re-suppressed on DTG/3TC; 1 withdrew, 1 had subsequent real time VL at 96 weeks.

## Most children re-suppressed following viral rebound

### DTG/3TC

11 children had confirmed  $VL \geq 50c/mL$

- 7 children re-suppressed to  $<50c/mL$  at 96w:
  - 3 on DTG/3TC
  - 3 on DTG-based 3DR
  - 1 on ATVr-based 3DR
- 4 not re-suppressed at 96w

### DTG-3DR

13 children had confirmed  $VL \geq 50c/mL$

- 9 children re-suppressed to  $<50c/mL$  at 96 weeks
- 1 child had confirmed VL rebound at 96w
- 3 not re-suppressed at 96w

## Similar number of children with SAEs or grade $\geq 3$ AEs in both arms

### Adverse events

- 15 SAEs in **11 children** in DTG/3TC vs 12 in **9 children** in DTG-3DR (P=0.646)
- 24 Grade  $\geq 3$  clinical AEs in **20 children** in DTG/3TC vs 15 in **11 children** in DTG-3DR (P=0.092)
- **“Infections and Infestations” system organ class had highest number of AEs**
- No ART-related SAEs; 1 ART related Grade  $\geq 3$  AE (low density lipoprotein increased) in DTG/3TC
- No ART modifying AEs

### Deaths, notable events & pregnancies

- 1 death in DTG/3TC (chronic cor pulmonale)
- 1 depression with suicidal ideation in DTG-3DR
- 2 pregnancies in DTG/3TC and 1 in DTG-3DR

## Proportions with emergent resistance mutations to DTG or NRTI were similar across arms

Major IAS-USA resistance mutations at confirmed VL  $\geq 50$  c/mL<sup>^</sup>:

➤ Major IN:

- ❖ DTG/3TC: 2/11, including 2/11 emergent [1 G140R\*; **1 G118R\***]
- ❖ DTG-3DR: 3/13, including 3/13 emergent [2 G140R\*; **1 G118R\***]

➤ Major NRTI:

- ❖ DTG/3TC: 3/10, including 1/7 emergent [**1 M184I\***; 1 M184V; 1 L74V V75I Y115F M184V]
- ❖ DTG-3DR: 3/9, including 1/6 emergent [**1 L74V\*** M184V; 1 M184V; 1 K70E# M184V#]

<sup>^</sup> Retrospective NGS testing on stored buffy coat samples; \* Emergent mutations; # No baseline resistance results – emergence cannot be established


Note: Mutations in **bold** confer intermediate to high-level resistance to relevant ARVs (**G118R** – DTG high-level; **M184V/I** – 3TC high-level; **L174V** – ABC intermediate)

# Acceptability

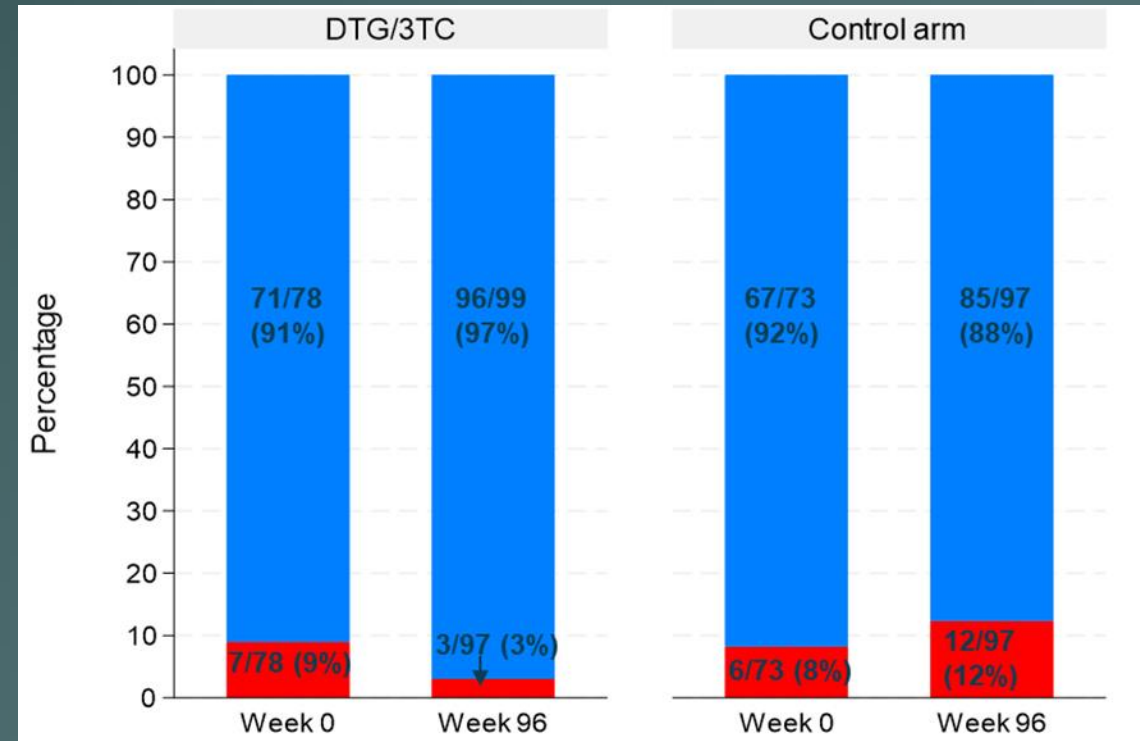
## Slightly higher overall participant satisfaction\* in the DTG/3TC arm

- “How happy you are with this medicine?”
- The majority were “happy” or “very happy” at baseline and 96 weeks:
  - **Baseline: 91% DTG/3TC vs 92% DTG-3DR**
  - **96w: 97% DTG/3TC vs 88% DTG-3DR,  $p=0.014$**  (Chi Squared test)

17. Please tell us overall how **happy** you are with this medicine(s). Please select **ONE** face that best describes how you feel.



Very unhappy    Unhappy    Neither happy nor unhappy    Happy    Very happy



Chi squared test at 96 weeks p-value: 0.014

Young person happiness  
■ Indifferent/Unhappy  
■ Happy/Very happy

\* Similar trend in the parent/carer report on how happy they think their child is at 96w, answer on an 11-point scale ( $p=0.094$ ; Wilcoxon rank sum test)

# Health Economics: Initial Findings



**Over 96 weeks, children on DTG/3TC had similar healthcare resource use and markedly lower ARV costs compared with those on DTG-3DR**

ARV costs on DTG/3TC were **~\$145 lower per child per year** (95% CI \$134 to \$154, 2025 USD).

**Total mean costs of healthcare services and antiretroviral therapy up to 96-week follow-up**

Cost item	Total mean cost (SD) (USD\$)		Incremental cost; mean (95% CI)
	DTG/3TC	Control	
<b>Total Healthcare Costs</b>	10 (14)	9 (4)	1 (-1, 3)
<b>ART drugs</b>	22 (13)	167 (69)	-145 (-154, -135)
<b>Total Costs</b>	33 (20)	176 (69)	-143 (-153, -133)

Note: all costs are presented in undiscounted 2025 US dollars. SD standard deviation; ART costs based on Global Fund pricing reference 2025

# Summary



- In children 2 to <15 years, DTG/3TC was non-inferior compared to DTG+2NRTI in maintaining virological suppression over 96-weeks
- Safety profile was similar
- Numbers with emergent resistance mutations to DTG and NRTIs were similar across arms
- Satisfaction with HIV treatment was high in both arms but marginally higher in the DTG/3TC arm
- Switching children who are virologically suppressed to DTG/3TC can save ~\$145 per child per year

**Children who are virologically suppressed on their first-line regimen can be switched to DTG/3TC**

# Acknowledgements and thanks



## D3 / Penta-21 team

- D3 participants and their families
- D3 main trial and substudies' investigators
- Trial Management Team
- Trial Steering Committee
- Data Monitoring Committee
- Youth Trial Board and all who supported community engagement
- Penta (sponsor)
- ViiV Healthcare (funder)

**Fondazione Penta ETS, Padova, Italy:** Carlo Giaquinto, Alessandra Nardone, Gabija Morkunaite

**MRC CTU at UCL:** Anna Turkova, Debbie Ford, Man Chan, Gabriela Toledo, Elizabeth James, Mags Thomason, Nazia Parkar, Iona White, Anna Parker, Anas Omar, Zainab Alkurwi, Moira Spyer, Katja Doerholt, Stephen Townsend, Hannah Sweeney, Margaret Hook, Alvin Daramola-Rose, Lee Barker, Lu Gao, Matteo Quartagno, Diana Gibb

**AMS – PHPT Research Collaboration, Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand:** Tim R. Cressey, Suwalai Chalermpanmetagul, Rukchanok Peongjakta, Ketwarin Pongkawong, Worathip Sriparaya, Warunee Khamjakkaew, Namthip Krueanual, Pra-ornsuda Sukrakanchana, Ampika Kaewbundit

**UGANDA: Baylor College of Medicine Children's Foundation:** Adeodata R. Kekiitiwa, Pauline Amuge, Christine Namugwanya, Lameck Kiyimba, Resty Babirye Okello, Florence Namuli, Ronald Nabimba, Angella Baita, Dickson Bbuye, Susan Tukamuhebwa, Rachael Namuddu Kikabi, Rose Jacqueline Kadhuba, Henry Balwa, Sarah Nabukalu, Muzamil Nsibuka Kisekka, Anthony Kirabira, Lekku Lawrence, Judith Tikabibamu, Maria Benita Aino, Gerald Agaba Muzorah, Collins Mujyanama, Annet Nalugo, Priscilla Namubiru; **Joint Clinical Research Centre:** Cissy Kityo, Victor Musiime, Elizabeth Kaudha, Annet Nanduudu, Henry Mugerwa, Caroline Otiye, Emmanuel Mujyambere, Dridah Nakiboneka, Barbara Mukanza, Julius Tumusiime, Onen Gilbert, Ritah Mbabazi, Abigail Atwine, Priscilla Kyobutungi, Juliet Ategeka, Alex Musiime, Sharif Musumba, Rashidah Nazzinda, Nicholas Wangwe, Phyllis Mwesigwa, Diana Rutebarika, Jameena Elsausko, Mangadalen Nansaigi, Mercy Tukamushaba, Alice Mulindwa, Aidah Nakalyango, Ocitti Paul, Christine Nambi, Milly Ndigendawani, Mariam Naabalamba, Eram David, Odochi Denis, Baliruno David, Ezra Lutalo, Eddie Rubanga, Josephine Namusanje, Josephine Kobusingye, Disan Mulima, Maria Nannungi, Faith Balmoi, Charles Draleku, Faith Mbasani, Crispus Katemba, Juliet Ankunda, Julian Tusiime, Benson Ouma Juma; **Makerere University – John Hopkins University Research Collaboration:** Philippa Musoke, Grace Miriam Ahimbisibwe, Hajira Kataike, Winnie Nansamba, David Balamusani, Rosemary Namwanje, Enoch Mulwany, Gerald Bright Businge, Maxensia Owor, Aziida Nabukeera, Ruth Nakku, Zainab Nakivumbi Nassoma, Immaculate Nayiga Serunjogi, Barbara Musoke Nakirya, Sarah Nakabuye, Erinah Kyomukama, Rebecca Wampamba, Stella Nalusiba, Emmanuel Mayanja, Donald Wagaana, Zaam Zinda Nakawungu, Sarah Babirye Ssebabi, Olivia Higiyo Kaboggoza, Edith Nabawubye, Mildred Kabasonga, Harriet Namusisi, Judith Nampewo, Agnes Mary Mugagga, Richard Isabirye, Francis Sserugo, Annet Kawuma, Agnes Namuddu, Joanita Nankya Baddokwaya, Juliet Nanyonjo, Winifred Kaahwa, Maria Musisi, Paula Mubiru Namayanja, Doreen Twenatwine, Robert Byuma, Winifred Luwedde, Margaret Mugenyi, Joseph Mutebo, Francis Katongole, Fabian Okello, Max Kiwewa, Ronald Okwera, Derick Balungi, Obed Tumwizere, Teopista Nakyanzi, Ann Kankindi, Maria Janine Nambusi, Ivan Rukundo, Henry Odyek, Barnabas Weere, Bosco Kafufu, David Ssebunya, Africano Kamugisha, Emmanuel Hakizimana, Charles Nyende, Evelyn Akurut, Johnson Tumwesigye, Brenda Catherine Kakayi, Rebecca Sakwa, Mark Ssenyonga, Joseph Semakula, Joyce Mwebaka, Judith Kaiza, Niscah Babirye Otim

**SOUTH AFRICA: Durban International Clinical Research Site, Enhancing Care Foundation:** Moherndran Archary, Rosie Mngqibisa, Tiyara Arumugam, Sundraprasen Pillay, Raziya Bobat, Nombuso Nkosi, Nozibusiso Rejoice Mosia, Sheleika Singh, Shingirai Chimene, Jabu Mkhulise, Innocentia Thandokuhle Mncube, Zethu Mnyandu, Michelle Moodley, Popi Shabalala, Simangele Bengu, Ida Elizabeth Mundhree; **Perinatal HIV Research Unit, Matlosana:** Ebrahim Variava, Tumelo Moloantsoa, Nadia Sabet, Ryan Sabet, Modiehi Mosala, Itumeleng Holele, Eva Mogotsi, Angelinah Montwedi, Serame Mokoena, Keabetswe Kotsokoane, Dineo Rampai, Avy Violari, Lerato Maretlwa, Palesa Tshipunyane, Iris Matotong, Abraham Mamwun Pattamukkil, Nkazimulo Xulu, Sthembiso Mhlanga, Ofhani Harmious Makhari, Gifty Okyere Manu, Zukisa Mpeluza, Tumelo Moloantsoa, Mbusiseni Ngema, Abdul Kaka, Rieta Stokes, Nadia Bellingan, Liniqwe Le Grange, Leoni Stytler, Zakkiyya Jeeva; **Perinatal HIV Research Unit, Soweto:** Avy Violari, Afaaf Liberty, Mandisa Nyati, Haseena Cassim, Sisinyana Ruth Mathiba, Lindiwe Maseko, Precious Ndebele, Jackie Brown, Emily Lebotsa, Deirdre Josipovic, Mantwa Kunene, Tryphinah Madonsela, Nasreen Abrahams, Zaakirah Essack, Zandisile Mtshali, Dipuo Dhlomoza, Thabile Degracia Hlomuka, Valerie Khemese

**THAILAND: Chiangrai Prachanukroh Hospital:** Pradthana Ounchanum, Suchada Ruenglerdpong, Areerat Kongponoi, Kanyanee Kaewmamueng, Warunee Srisuk, Yupawan Thaweasombat, Sukanda Denjanta, Jutarat Thewsoongnoen, Naowarat Kanyanone; **Kalasin Hospital:** Sakulrat Srirojana, Doungjai Donngern, Petcharat Phunkhum, Arisara Kamkoonmongkol, Thananya Naksomboon, Nonthaporn Na Kalasin; **Khon Kaen Hospital:** Ussanee Sriropotong, Athiporn Rungsapphaiboon, Wallapa Daechasatoin, Wachalerm Boonsub, Patamawadee Sudaard, Thunyasiri Dechboran, Manthana Mitchai, Thanawat Samranphit, Orapin Wannasri, Kriangkrai Kongsuk; **Nakornping Hospital:** Suparat Kanjanavanit, Rujirek Kamolrattana, Thannapat Chankun, Jiraporn Punyayen, Chayakorn Saewtrakool, Pacharaporn Yingyong, Raungwit Junkaew, Benjawan Thomyota; **Prapokklao Hospital:** Kanokkorn Sawasdichai, Chaiwat Ngampiyaskul, Nantika Paiboon, Benjama I-nala, Wanna Chamjamrat, Pisut Greetanukroh, Chanthaporn Imbumroong, Sasipass Khannak, Rattana Chahmeanprabnakorn

**UK: Birmingham Heartlands Hospital:** Steven Welch, Ezgi Seager, Yvonne Beuvink, Melanie Rooney, Laura Thrasyvoulou, Katie Price, George Gavin, Sue Fagg, Baldip Kaur, Molly Williams; **Great Ormond Street Hospital, UK:** Anna Turkova, Alasdair Bamford, Delane Shingadia, Jade Sugars, Olamide Alimi, Carolyn Chan, Kelly Cripps, Sabina Zahed, John Koroma

**SPAIN: Hospital Sant Joan de Déu:** Clàudia Fortuny, Antoni Noguera-Julian, Anna Vazquez Marchan, Cristina López Hidalgo, Sílvia Cuadras Ferrando, Alba Murciano, Miriam Coto, Kenia Sánchez, Bonaventura Ruiz; **Hospital Universitario 12 de Octubre:** Pablo Rojo, Cristina Epalza, Luis Prieto, Jose Tomas Ramos, Ianire Gallego, Verónica Martín, Lilit Manukyan, Manuel Gijon

**PK substudies:** David Burger, Angela Colbers, Tom Jacobs, Lisanne Bevers; **Pharmacogenomics substudy:** Dan Carr, Andrew Owen, Rebecca Jensen; **Virology substudy:** Eleni Nastouli, Moira Spyer, Matt Byott, Ian Botha; **Health Economics substudy:** Paul Revill, Simon Walker, Sarah Ronaldson;

**Youth Trials Board:** Magda Conway, Lungile Jafta, Mercy Shibemba; **Trial Steering Committee Members:** Hermione Lyall, Elizabeth Maleche Obimbo, Theodore Ruel, Alex Compagnucci, Imelda Mahaka, Fanele Bulose, Gugulethu Bomela, Anna Turkova, Cissy Kityo, Tim Cressey, Avy Violari; **Data Monitoring Committee Members:** Anton Pozniak, Jane Crawley, Rodolphe Thiébaud, Helen McIlleron (for consideration of PK substudy)

# What do young people think?



If DTG/3TC works as well as 3-drug ART should be offered DTG/3TC?



“only one tablet - easier to take”

“less side effects than with 3 drugs”

“less medications (toxins) in the body”

Should DTG/3TC also be studied in children starting ART,  
or can we extrapolate from adults?



“children’s bodies are different to adults”

“biologically and clinically different”

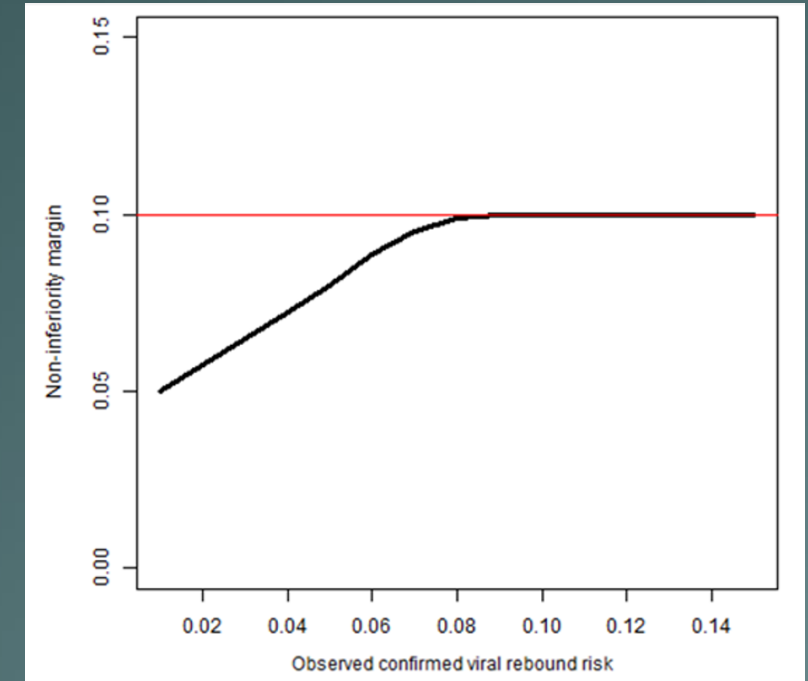
“different immune systems”

**Additional slides**

# SAFE non-inferiority frontier



- Employed a ‘smooth away from expected’ (SAFE) non-inferiority frontier\*
- The choice of NI margin depends on the observed proportion of children in the control arm with confirmed viral rebound (table)
- The smaller the observed proportion in the control group, the smaller the NI margin (fig)
- If the observed viral rebound in the control arm <9%, 99%CI is employed to control for type 1 error resulting from change in NI margin



Pre-specified CI and NI margin depending on the observed VL rebound in Control

Observed control VL rebound proportion	1%	2%	3%	4%	5%	6%	7%	8%	9%	10%	11%	12%	13%	14%	15%
NI Margin	5.0%	5.8%	6.5%	7.3%	8.0%	8.9%	9.5%	9.9%	10.0%						
Confidence interval (CI)	99%								95%						

\*Quartagno et al. Trials 2023