Virological failures and genotypic resistance in children and adolescents randomised to dolutegravir-based ART vs. standard-of-care in the ODYSSEY trial

Alasdair Bamford on behalf of the ODYSSEY trial team

IMPAACT MEETING, 23rd October 2023

ODYSSEY virology subpopulation at baseline (n=788)

Baseline characteristics

- Age, median [range]: 11.4 years [8-14.6]
- 51% female

Baseline ART

NRTI backbone

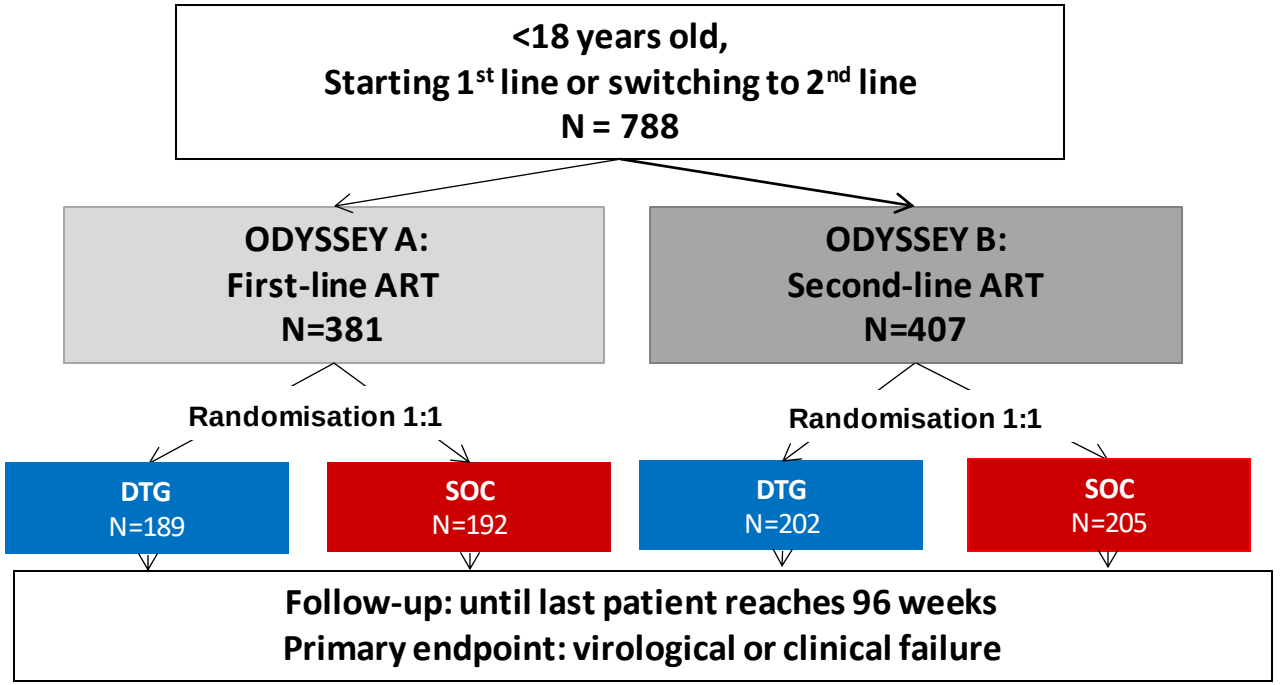
ODYSSEY A – first-line	ODYSSEY B – second-line
83% ABC+3TC	53% ABC+3TC
16% TDF+XTC	26% TDF+XTC
1% ZDV+3TC	20% ZDV+3TC
	1% ABC+TDF

Third agents in the SOC arm

ODYSSEY A: first-line 77% EFV, 17% LPV/r, 3% NVP

ODYSSEY B: second-line 71% LPVr, 24% ATVr

- A randomised 96-week non-inferiority trial comparing **DTG-based ART with standard-of-care** in children **starting first- or second-line ART**



Penta

Resistance sub-study

Participants with virological failure* by 96 weeks

	DTG	SOC
ODYSSEY A: first-line	18 (10%)	43 (22%)
ODYSSEY B: second-line	33 (16%)	43 (21%)

Definition: virological failure

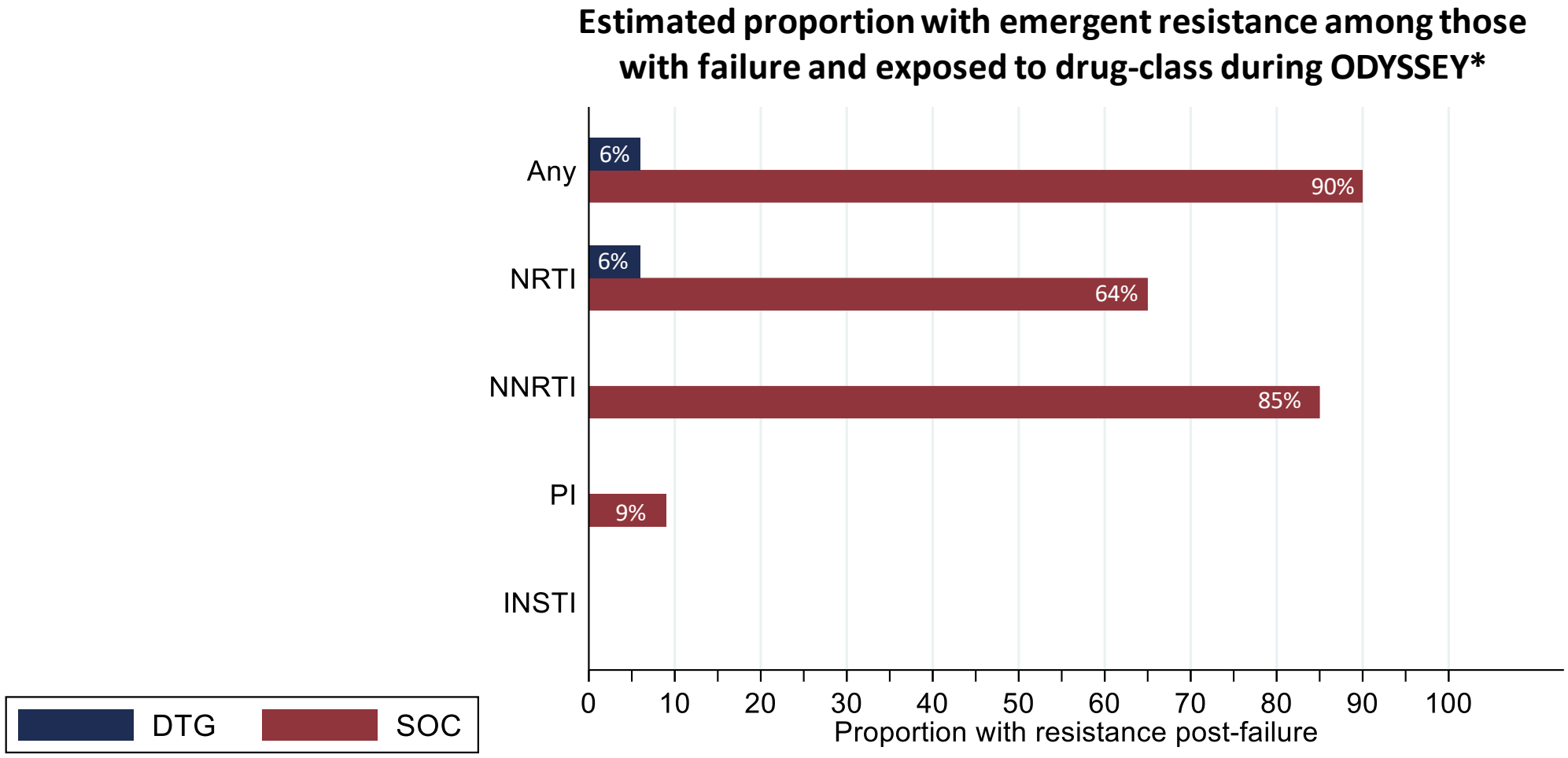
- <1 log drop at w24 and ART switch for treatment failure
- confirmed (x2) VL ≥ 400 c/mL at any time after w36

*Virological failure main component of trial primary endpoint

Resistance testing

- Participants with virological failure were retrospectively tested for post-failure resistance up to week 96 (Sanger sequencing)
- Requested the latest sample with VL≥1000c/mL after failure and prior to treatment change (if occurred)
- Earlier samples, including baseline, were sequenced if ≥1 major IAS mutation was identified in post-failure sample
- Drug resistance mutations were defined according to IAS major mutations list (2019)
- Drug susceptibility was defined according to the Stanford HIVdb algorithm 9.0

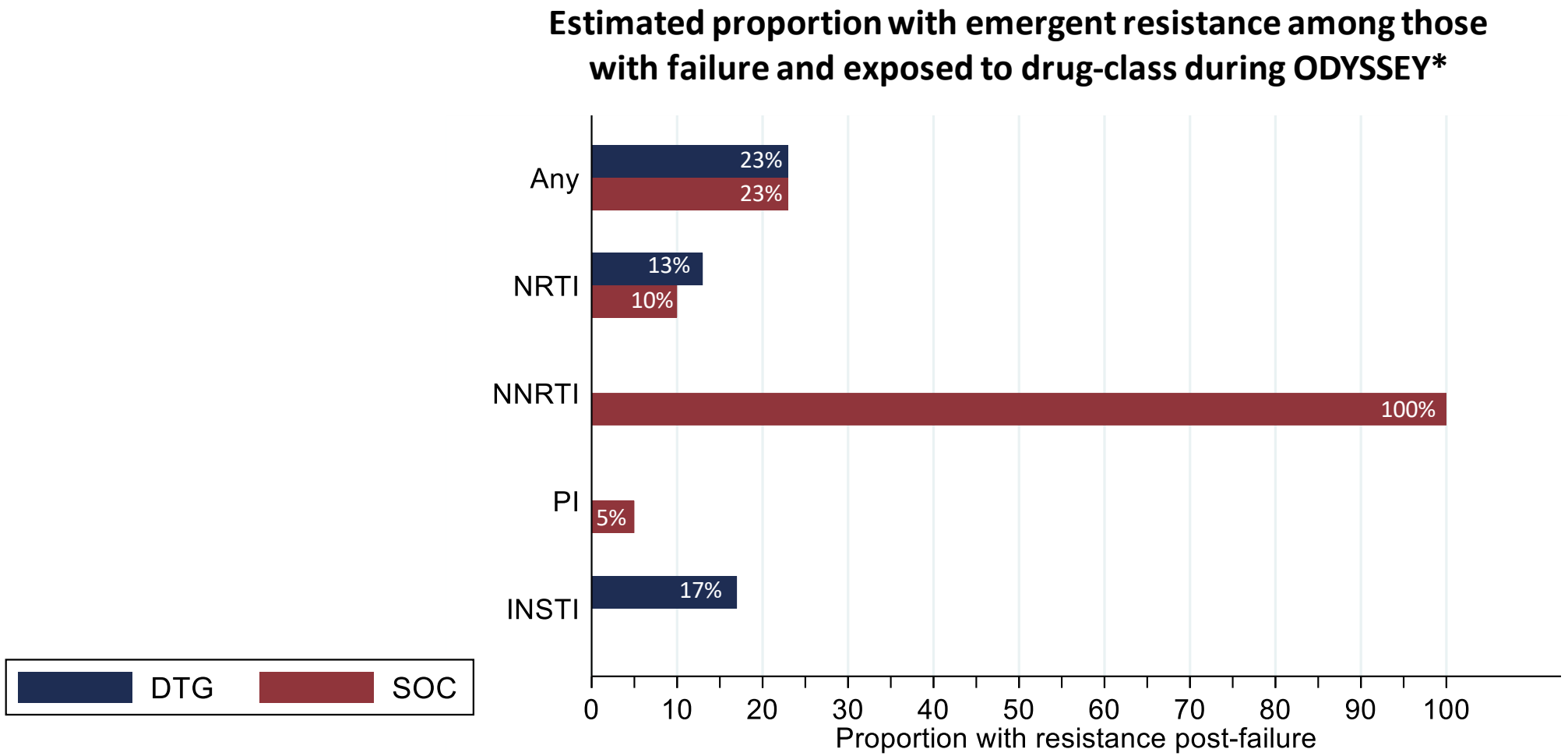
ODYSSEY A:
Emergent resistance among those failing first-line



*Estimated in participants failing drug class, using multiple imputation to account for missing resistance tests at baseline and/or post-failure

Penta

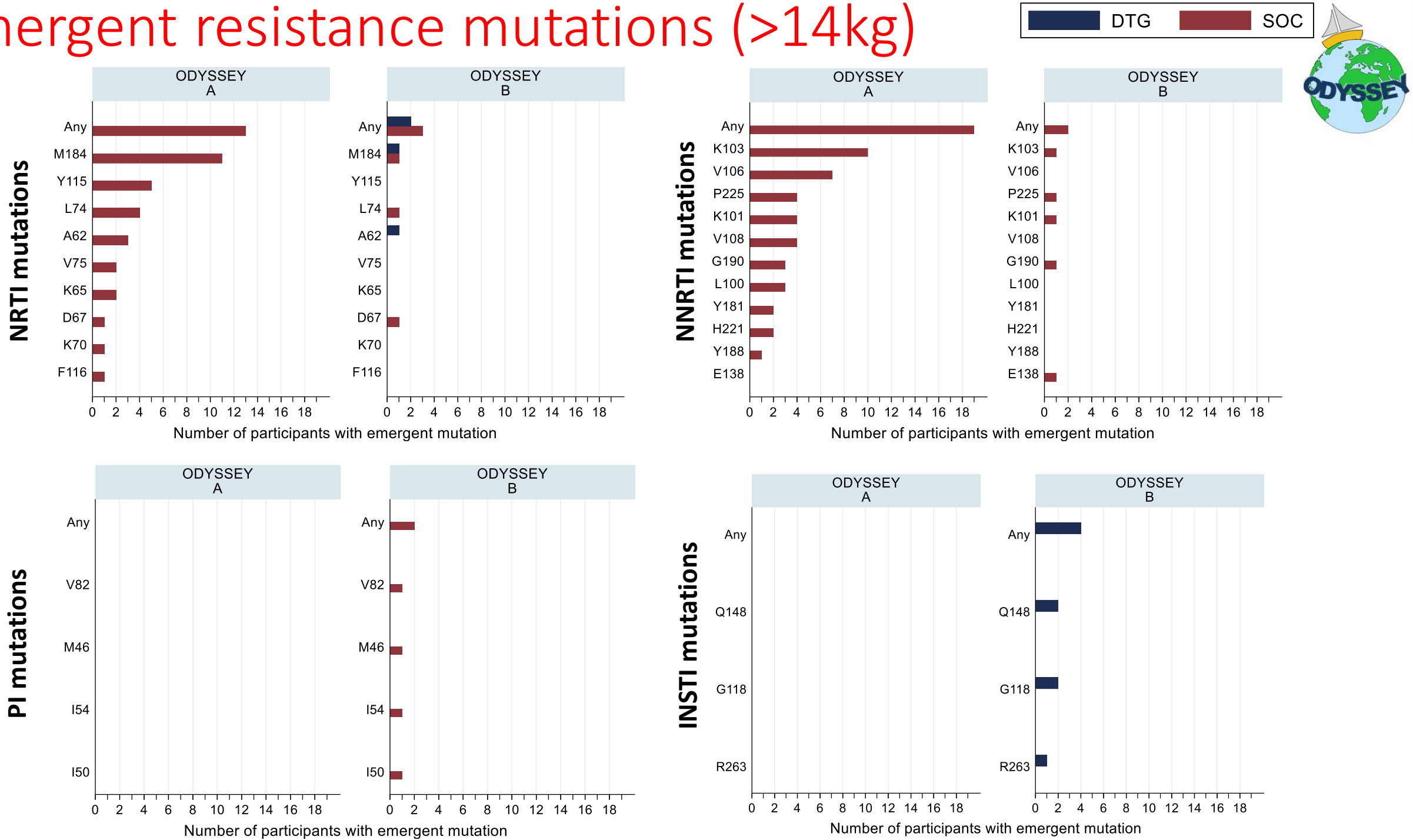
ODYSSEY B:
Emergent resistance among those failing second-line



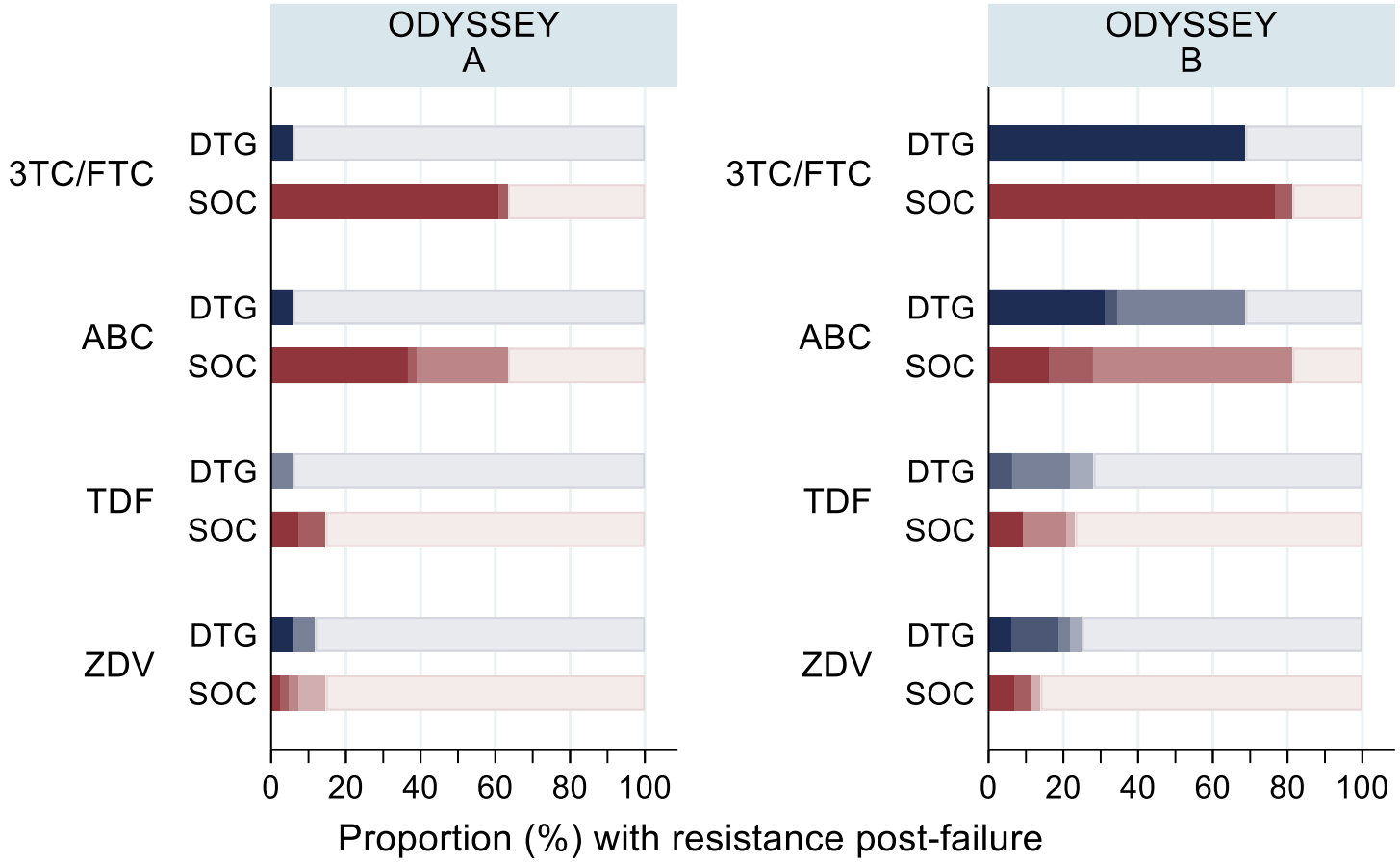
*Estimated in participants failing drug class, using multiple imputation to account for missing resistance tests at baseline and/or post-failure

Penta

Emergent resistance mutations (>14kg)



Estimated NRTI resistance predicted using Stanford algorithm among those with failure

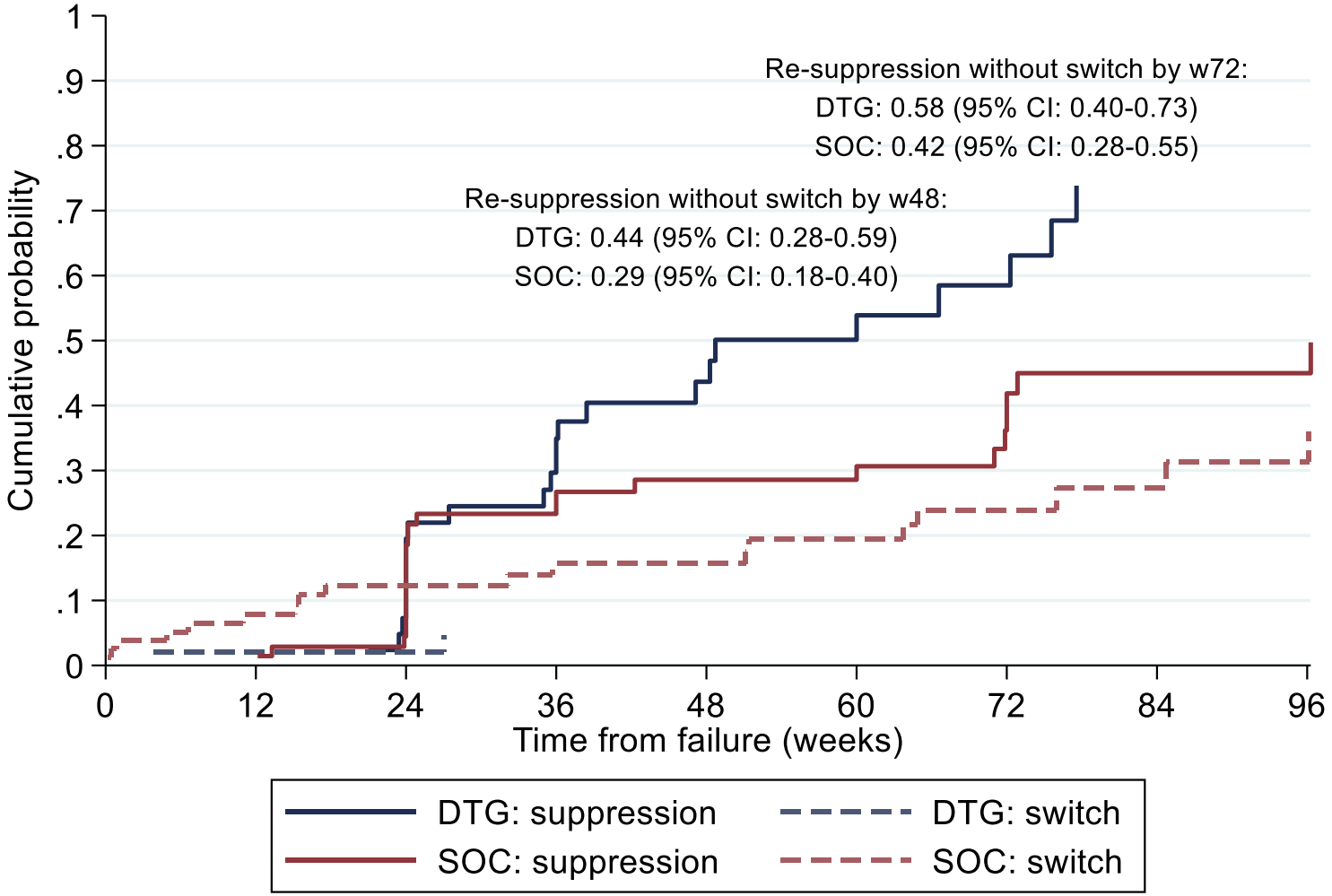


Resistance key:

DTG: high-level | intermediate | low-level | potential low-level | susceptible

SOC: high-level | intermediate | low-level | potential low-level | susceptible

Time to re-suppression without ART switch following virological failure



Adjusted cause-specific HR for suppression comparing DTG vs. SOC: 1.99 (95% CI: 1.18-3.37), P=0.01

No significant evidence of different treatment effects on first line (ODYSSEY A) vs. second line (ODYSSEY B): P=0.099

Re-suppression: 2 consecutive VLs<400c/ml

ART switch: switch in any drug due to treatment failure or switch in 3rd agent due to toxicity, pregnancy, or protocol deviation

Penta

Summary

- ODYSSEY demonstrated that DTG has a high genetic resistance barrier in children, preventing emergent resistance to NRTIs on first-line ART
- We identified minimal post-failure resistance to any drug class amongst children initiating first-line DTG, significantly less than on first-line SOC
- Among those on second-line DTG, 5 children developed new INSTI resistance
  - 4/5 were on zidovudine backbone
- A high proportion of children re-suppress after virological rebound without ART switch, with marginally higher rates with DTG
  - 1/5 with INSTI resistance had re-suppressed by end of trial
- Baseline ABC resistance level had minimal impact on VF rates in those on DTG/ABC/XTC*
- **These results support using DTG-containing regimens for children starting first-line or second-line ART, but ongoing adherence support is required, especially on second-line**

*data not shown

Thank you

- ODYSSEY participants
- ODYSSEY investigators
- Trial Management Team
- Trial Steering Committee
- Data Monitoring Committee
- Endpoint Review Committee
- Penta (sponsor)
- ViiV Healthcare (funder)
- Mylan

The ODYSSEY Trial Team

(MRC CTU at UCL) Shabinah Ali, Abdel Babiker, Chiara Borg, Anne-Marie Borges Da Silva, Joanna Calvert, Deborah Ford, Joshua Gasa, Diana M. Gibb, Nasir Jamil, Sarah Lensen, Emma Little, Fatima Mohamed, Samuel Montero, Cecilia L. Moore, Rachel Oguntimehin, Anna Parker, Reena Patel, Tasmin Phillips, Tatiana Sarfati, Karen Scott, Clare Shakeshaft, Moira Spyer, Margaret Thomason, Anna Turkova, Rebecca Turner, Nadine Van Looy, Ellen White, Kaya Widuch, Helen Wilkes, Ben Wynne.
(PENTA-ID) Carlo Giaquinto, Tiziana Grossele, Daniel Gomez-Pena, Davide Bilardi, Giulio Vecchia.
(INSERM-ANRS) Alexandra Compagnucci, Yacine Saidi, Yoann Riault, Alexandra Coelho, Laura Picault, Christelle Kouakam.
(PHPT) Tim R. Cressey, Suwalai Chalermpantmetagul, Dujrudee Chinwong, Gonzague Jourdain, Rukchanok Peongjakta, Pra-ornsuda Sukrakanchana, Wasna Sirirungsi.
(Sub-study Partners) Janet Seeley, Sarah Bernays, Magda Conway, Nigel Klein, Eleni Nastouli, Anita De Rossi, Maria Angeles Munoz Fernandez, David Burger, Pauline Bollen, Angela Colbers, Hylke Waalewijn.
(Joint Clinical Research Centre, Uganda) Cissy M. Kityo, Victor Musiime, Elizabeth Kaudha, Annet Nanduudu, Emmanuel Mujyambere, Paul Ocitti Labeja, Charity Nankunda, Juliet Ategeka, Peter Erim, Collin Makanga, Esther Nambi, Abbas Lugemwa, Lorna Atwine, Edridah Keminyeto, Deogratiuos Tukwasibwe, Shafic Makumbi, Emily Ninsiima, Mercy Tukamushaba, Rogers Ankunda, Ian Natuhurira, Miriam Kasozi, Baker Rubinga. **(Baylor College of Medicine Children's Foundation, Uganda)** Adeodata R. Kekitiinwa, Pauline Amuge, Dickson Bbuye, Justine Nalubwama, Winnie Akobye, Muzamil Nsibuka Kisekka, Anthony Kirabira, Gloria Ninsiima, Sylvia Namanda, Gerald Agaba, Immaculate Nagawa, Annet Nalugo, Florence Namuli, Rose Kadhuba, Rachael Namuddu, Lameck Kiyimba, Angella Baita, Eunice Atim, Olivia Kobusingye, Clementine Namajja, Africanus Byaruhanga, Rogers Besigye, Herbert Murungi, Geoffrey Onen. **(MUJHU Research Collaboration, Uganda)** Philippa Musoke, Linda Barlow-Mosha, Grace Ahimbisibwe, Rose Namwanje, Monica Etima, Mark Ssenyonga, Robert Serunjogi, Hajira Kataike, Richard Isabirye, David Balamusani, Monica Nolan. **(FAM-CRU, South Africa)** Mark F. Cotton, Anita Janse van Rensburg, Marlize Smuts, Catherine Andrea, Sumaya Dadan Sonja Pieterse, Vinesh Jaeven, Candice Makola, George Fourie, Kurt Smith, Els Dobbels, Peter Zuidewind, Hesti Van Huyssteen, Mornay Isaacs, Georgina Nentsa, Thabis Ncgaba, Candice MacDonald, Mandisa Mtshagi, Maria Bester, Wilma Orange, Ronelle Arendze, Mark Mulder, George Fourie. **(PHRU, South Africa)** Avy Violari, Nastassja Ramsagar, Afaaf Liberty, Ruth Mathiba, Lindiwe Maseko, Nakata Kekane, Busi Khumlo, Mirriam Khunene, Noshalaza Sbisi, Jackie Brown, Ryphina Madonsela, Nokuthula Mbadaliga, Zaakirah Essack, Reshma Lakha, Aasia Vadee, Derusha Frank, Nazim Akoojee, Maletsatsi Monametsi, Gladness Machache, Yolandie Fourie, Anusha Nanan-kanjee, Juan Erasmus, Angelous Mamiane, Tseleng Daniel, Fatima Mayat, Nomfundo Maduna, Patsy Baliram. **(Prapokklao Hospital, Thailand)** Chaiwat Ngampiyasakul, Pisut Greetanukroh, Wanna Chamjamrat, Praechadaporn Khannak. **(Phayao Hospital, Thailand)** Pornchai Techakunakorn, Thitiwat Thapwai, Patcharee Puangmalai, Ampai Maneekaew. **(Chiangrai Prachanukroh Hospital, Thailand)** Pradthana Ounchanum, Yupawan Thaweesombat, Areerat Kongponoi, Jutarat Thewsoongnoen. **(Nakornping Hospital, Thailand)** Suparat Kanjanavanit, Pacharaporn Yingyong, Thida Namwong, Rangwit Junkaew. **(Khon Kaen Hospital, Thailand)** Ussanee Srirompotong, Patamawadee Sudsaard, Siripun Nuanbuddee, Sookpanee Wimonklang. **(Mahasarakam Hospital, Thailand)** Sathaporn Na-Rajsima, Suchart_Thongpaen, Pattira Runarassamee, Watchara Meethaisong, Arttasid Udomvised. **(Klerksdorp Tshepong Hospital Complex, South Africa)** Ebrahim Variava, Modiehi Rakgokong, Dihedile Scheppers, Tumelo Moloantoa, Abdul Hamid Kaka, Tshepiso Masienyane, Akshmi Ori, Kgosimang Mmolawa, Pattamukkil Abraham. **(Durban International Clinical Research Site, South Africa)** Moherndran Archary, Rejoice Mosia, Sajeeda Mawlana, Rosie Mngqibisa, Rashina Nundlal, Elishka Singh, Penelope Madlala, Allemah Naidoo, Sphiwee Cebekhulu, Petronelle Casey, Collin Pillay, Subashinie Sidhoo, Minenhle Chikowore, Lungile Nyantsa, Melisha Nunkoo, Terence Nair, Enbavani Pillay, Sheleika Singh, Sheroma Rajkumar. **(AHRI, South Africa)** Osee Behuhuma, Olivier Koole, Kristien Bird, Nomzamo Buthelezi, Mumsy Mthethwa. **(UZCRC, Zimbabwe)** James Hakim, Hilda Mujuru, Kusum Nathoo, Mutsa Bwakura-Dangarembizi, Ennie Chidziva, Shepherd Mudzingwa, Themelihle Bafana, Colin Warambwa, Godfrey Musoro, Gloria Tinago, Shirley Mutsai, Columbus Moyo, Ruth Nhema, Misheck Nkalo Phiri, Stuart Chitongo, Joshua Choga, Joyline Bhiri, Wilber Ishemunyoro, Makhosonke Ndlovu. **(HIVNAT, Thailand)** Thanyawee Puthanakit, Naruporn Kasipong, Sararut Chanthaburanun, Kesdao Nanthapisal, Thidarat Jupimai, Thornthun Noppakaorattanamanee, Torsak Bunupuradah, Wipaporn Natalie Songtaweesin, Chutima Saisaengjan. **(European Site Investigators)** Stephan Schultze-Straber, Christoph Konigs, Robin Kobbe, Felicia Mantkowski, Steve Welch, Jacqui Daglish, Laura Thrasyvoulou, Delane Singadia, Sophie Foxall, Judith Acero, Gosia Pasko-Szcech, Jacquie Flynn, Gareth Tudor-Williams, Farhana Abdulla, Srini Bandi, Jin Li, Sean O'Riordan, Dominique Barker, Richard Vowden, Colin Ball Eniola Nsirim, Kathleen McClughlin, India Garcia, Pablo Rojo Conejo, Cristina Epalza, Luis Prieto Tato, Maite Fernandez, Luis Escosa Garcia, Maria José Mellado Peña, Talia Sainz Costa, Claudia Fortuny Guasch, Antoni Noguera Julian, Carolina Estepa, Elena Bruno, Alba Murciano Cabeza, Maria Angeles Muñoz Fernandez, Paula Palau, Laura Marques, Carla Teixeira, Alexandre Fernandes, Rosita Nunes, Helena Nascimento, Andreia Padrao, Joana Tuna, Helena Ramos, Ana Constança Mendes, Helena Pinheiro, Ana Cristina Matos.
(Local Site Monitors) Flavia Kyomuhendo, Sarah Nakalanzi, Cynthia Mukisa Williams, Ntombenhle Ngcobo, Deborah Pako, Jacky Crisp, Benedictor Dube, Precious Chandiwana, Winnie Gozhora.
(Independent Trial Steering Committee Members) Ian Weller, Elaine Abrams, Tsitsi Apollo, Polly Clayden, Valériane Leroy. **(Independent Data Monitoring Committee Members)** Anton Pozniak, Jane Crawley, Rodolphe Thiébaut, Helen McIlleron. **(Endpoint Review Committee Members)** Alasdair Bamford, Hermione Lyall, Andrew Prendergast, Felicity Fitzgerald, Anna Goodman.

Funding. The study received funding from ViiV Healthcare. The MRC Clinical Trials Unit at UCL receives core support from the UK Medical Research Council (grant number MC_UU_12023/26). INSERM-ANRS supports the trial in France. The PENTA Foundation provides support to sites in Europe. The funders had no direct role in the preparation of the presentation. ViiV Healthcare and Mylan donated study drugs.

Penta