Viral suppression, viral failure and safety outcomes in children and adolescents on dolutegravir (DTG) in Europe and Thailand

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on behalf of the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC)

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Disclosure

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Summary

What is your main question?

What is the effectiveness and safety of DTG in children and adolescents living with HIV in routine care settings in Europe and Thailand?

What did you find?

- Overall ~90% were virally suppressed throughout time on DTG but there were variations by ART and viral load status at DTG start
- DTG was generally well tolerated with low rates of safety events

Why is it important?

Large multi-country cohort with early access to DTG provide supporting evidence of the safety and effectiveness of DTG at up to 4 years in children and adolescents

Background and aim

- Dolutegravir (DTG) recommended by WHO for 1st and subsequent-line ART in children and adolescents living with HIV (CALHIV) since 2021.
- Large randomised clinical trials in CALHIV on DTG:
  - ODYSSEY (n=792, 1st/2nd line): 81% viral load (VL) <50c/mL on DTG at 96 weeks[1]
    20% had viral or clinical failure by week 192[2]
  - CHAPAS-4 (n=919, 2nd line): 83% VL <60 c/mL on DTG at 96 weeks[3]
- Large observational cohorts in sub-Saharan Africa reported 85-93% viral suppression across different settings but had limited follow up (<24 months), safety data, no estimate of viral failure[4-6]
- Few studies in Europe reported safety and effectiveness outcomes but with small sample (n<150)[7]

Aim: To assess the effectiveness and safety of DTG in CALHIV in Europe and Thailand

1. Turkova, NEJM 2021; 2. Mujuru, CROI 2024; 3. Bwakura-Dangarembizi, MedRxiv 2024; 4. Bacha, PIDJ 2023; 5. Devendra, AIDS 2024; 6. Gill, PIDJ 2023; 7. Frange, HIVMed 2019

European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC)

Long standing cohort collaboration - pools data on complete clinical and treatment history of CALHIV. This study included data from 15 cohorts in 12 countries

Inclusion criteria: age <18 years at DTG start

Data cut-off date: May 2023

Methods: Effectiveness

i. Proportion with **viral suppression** (VL<50c/mL) after 24, 48, 96, 144 and 192 (+/-12) weeks

ii. Cumulative incidence of **viral failure (VF);** defined as 2 consecutive VLs ≥400c/mL or 1 VL ≥400c/mL + DTG discontinuation <4 months) after 24wks.

- Outcomes overall & by ART and VL status at DTG start for i. and ii.

iii. Cox proportional hazards models to assess **factors associated with VF** (adjusted a priori for age, sex and ART/VL status)

Factors examined: age, sex, ART/VL status, previous treatment failure (derived from reason for ART change reported by cohorts), WHO immune stage, region

Censoring: earliest of last visit, death, or discontinuation

Methods: Safety

Safety outcomes

i. **Adverse events (AE):** frequency of AEs and serious AEs (SAEs)
ii. **Laboratory abnormalities:** rates of DAIDS grade ≥3 per 100 person years
iii. **Discontinuation**: cumulative incidence of discontinuation of DTG (all-cause)

Censoring: discontinuation date +30 days

Results: Characteristics at DTG start

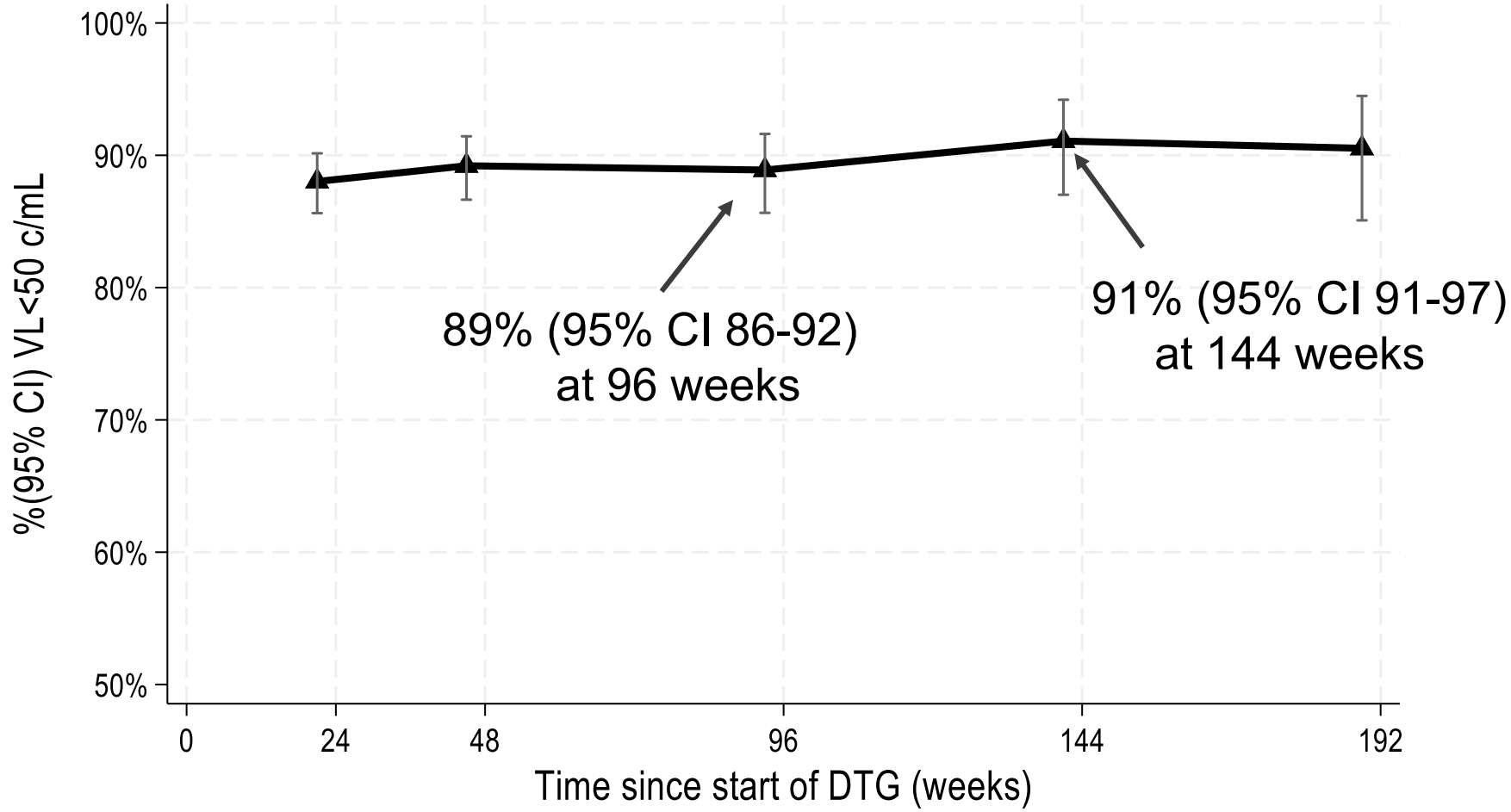
Characteristic		Total (n=1231)
Female		607 (50%)
Median age (years)		14 [11, 16]
Perinatal HIV		1020 (95%)
Ethnicity	Black	520 (42%)
	White	451 (37%)
	Asian	130 (11%)
	Other	105 (9%)
Region	UK/Ireland	382 (31%)
	Ukraine	282 (23%)
	Spain	198 (16%)
	Rest of Europe	269 (22%)
	Thailand	100 (8%)

Characteristic		Total (n=1231)
ART & VL Status	ART-naïve	120 (10%)
	ART-experienced VL≥200c/mL	163 (13%)
	ART-experienced VL<200c/mL	603 (49%)
	ART-experienced unknown VL	345 (28%)
Median duration on ART (years)		9 [5, 12]
Median CD4 count		710 [492, 973]
Advanced/severe WHO immune stage for age		127 (14%)
Median calendar year		2018 [2017, 2020]
Median duration on DTG (weeks)		93 [49, 163]

Characteristics presented among those with data available. Variables with >10% of missing data were HIV acquisition mode (13%), CD4 count (26%) and WHO immune stage for age (26%)

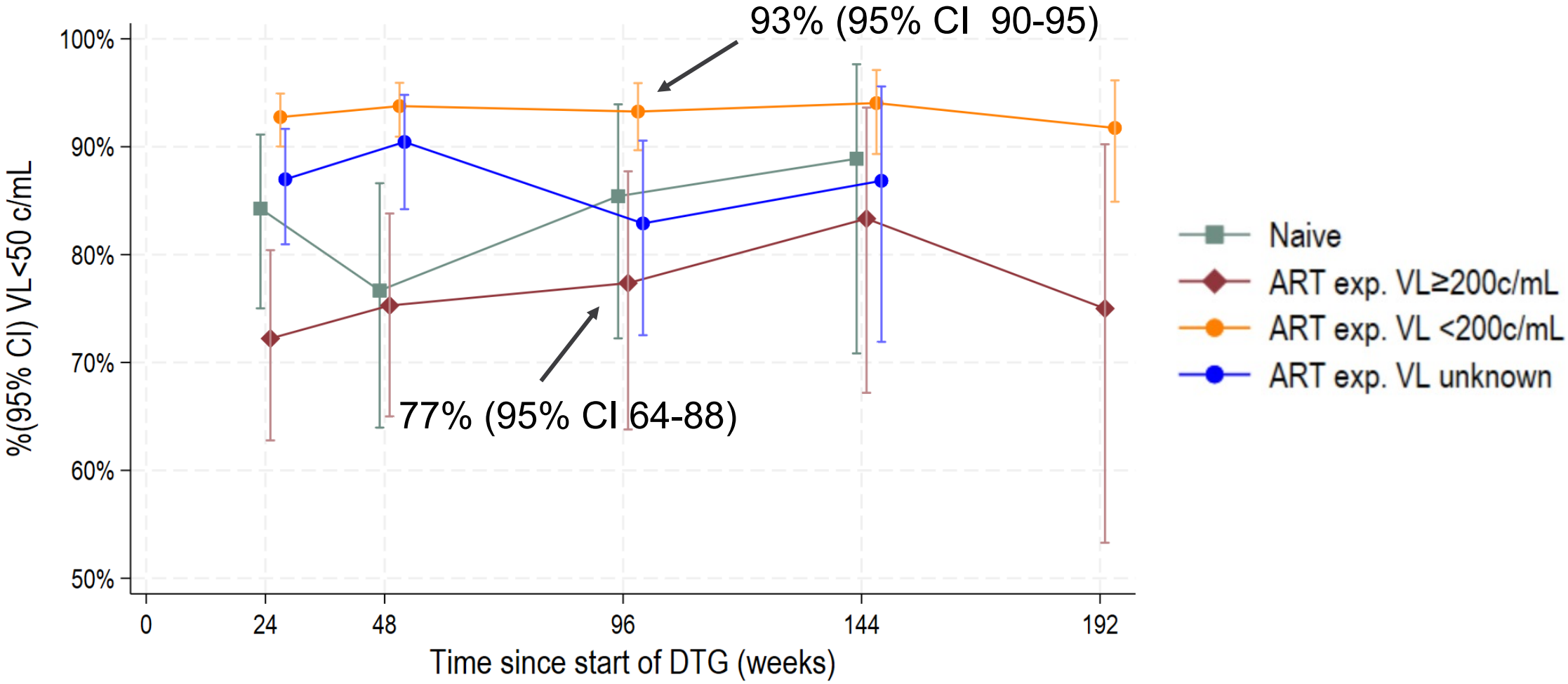
Viral suppression (<50 c/mL) overall

Overall: 88-92% were virally suppressed <50c/mL at 24-192 weeks

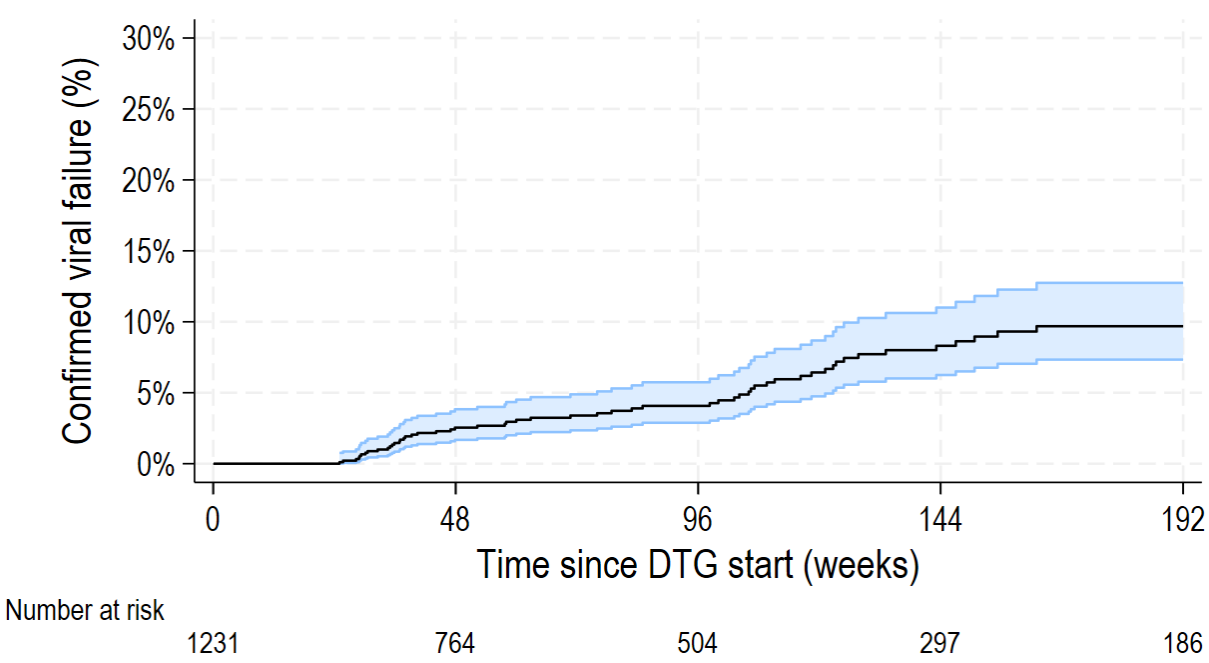


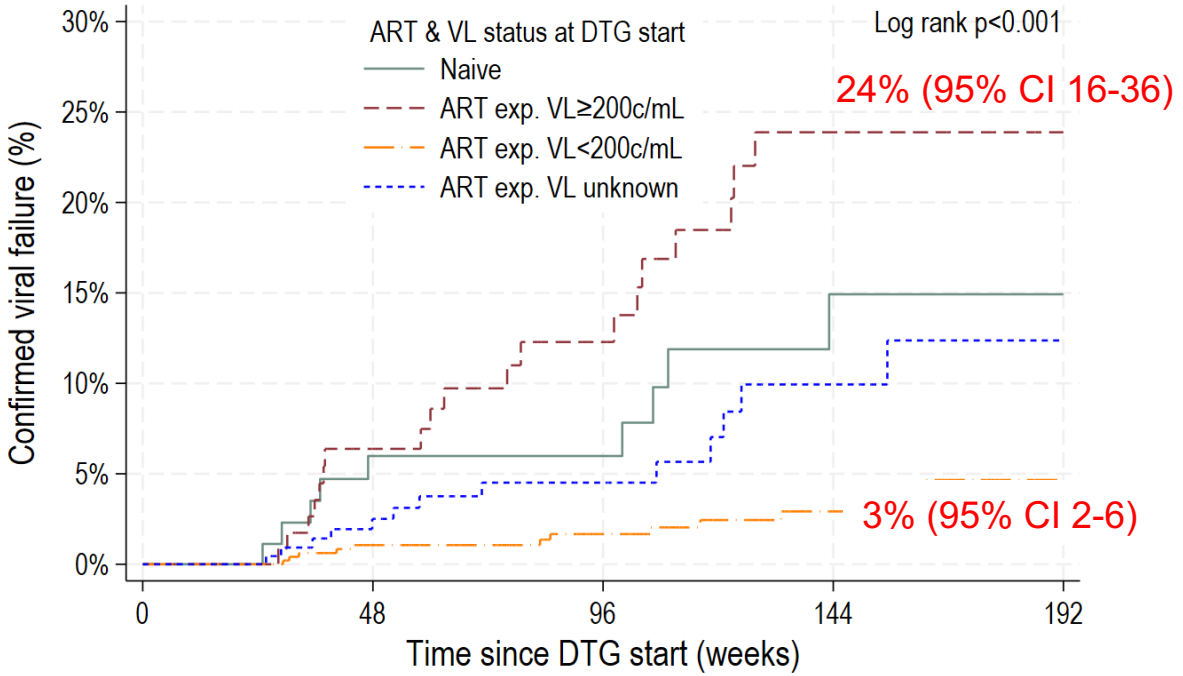
Viral suppression by ART and VL status at DTG start

Over 70% suppressed in all subgroups but significant variation



Cumulative incidence of viral failure





- 58/778 (7%) experienced VF
- Median time to VF: 81 [IQR 31,123] wks

- 4.1% (95% CI 2.9-5.7) by 96 wks
- 8.3% (95% CI 7.3-11.0) by 144 wks

After adjusting for age, sex and ART/VL status: **female sex**, **treatment experienced and viraemic**, **advanced/severe WHO immune stage**, **previous treatment failure** and **UK/Ireland region** were associated with **higher risk of VF (all p<0.05).**

Safety

- Of 1146/1231 (93%) with clinical data:
  - 26 (2.3%) had 52 AEs **causally related* to DTG,** including **5 SAEs** (headache, grade 3 raised creatinine, psychiatric disturbance, renal colic and a neurological event):
    - 5 patients had 25 AEs related to elevated labs
    - 7 patients had 8 neurological/neuropsychiatric AEs
  - **No deaths**

- Of 848/1231 (69%) with laboratory data, 46 CALHIV (5.4%) had 57 **DAIDS grade 3/4 events** on DTG

- Cumulative incidence of **all-cause discontinuation:** 5% (4,7) by 96 weeks and 10% (8,12) by 144 weeks

*possible, probable or definite according to treating clinician

Conclusion

- Most CALHIV **on DTG in the EPPICC network** were **treatment-experienced adolescents at start of DTG.**
- Overall **~90% were virally suppressed throughout follow up time** on DTG, comparable to ODYSSEY and CHAPAS-4 findings albeit different characteristics.
- **Low incidence of viral failure** except for those **ART experienced and viraemic** at DTG start, where ~ a quarter experienced viral failure by 144 weeks and warrants further monitoring and highlights the need for access to effective treatments after DTG failure
- DTG was **generally well tolerated** with **low rates of laboratory grade ≥3 events** and **low numbers of SAEs,**

Growth on DTG see Crichton et al. at AIDS (#TUPEB086)

Factors associated with VF on DTG see Scott et al. #4 at International Workshop on Pediatrics & HIV 2024

Safety and effectiveness on TAF see Chappell et al. at AIDS (#WEPEB124)

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Cohorts (principal investigators) included in analysis:

- Belgium: Hospital St Pierre Cohort, Brussels (Tessa Goetghebuer)
- Denmark: Denmark Copenhagen Cohort (Thomas Hoffman)
- Germany: German Pediatric and Adolescent HIV Cohort (Christoph Königs)
- Greece: Greek cohort (Vana Spoulou)
- Italy: Anna Meyer Children's University Hospital, Florence (Luisa Galli)
- Poland: Polish paediatric cohort (Magdalena Marczynska)
- Romania: "Victor Babes" Hospital Cohort, Bucharest (Luminita Ene)
- Spain: CoRISPE-cat, Catalonia (Antoni Noguera Julian)
- Spain: CoRISPES, rest of Spain (Marisa Navarro, Pablo Rojo Conejo, Jose Tomas Ramos Amado)
- Sweden: Swedish Cohort Study (Lars Naver)
- Switzerland: Swiss Mother and Child HIV Cohort Study (Christian Kahlert)
- Thailand: Chulalongkorn University (Thanyawee Puthanakit)
- Thailand: Khon Kaen Hospital Cohort (Nattakarn Tantawarak)
- Ukraine: Paediatric HIV Cohort (Ruslan Malyuta, Alla Volokha)
- UK & Ireland: Collaborative HIV Paediatric Study (Ali Judd)

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