Evaluation of Cross-Sectional HIV Incidence Recency Testing in Samples from the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial

EPC0319

Scan for more information and a plain language summary of this poster

Stephanie Cox[1], Yongwu Shao[1], Helen Rees[2], Sally Demirdjian[1], Kristen Andreatta[1], Kate B Heller[3], Anurag Nekkalapudi[1], Christoph Carter[1], Moupali Das[1], Pearl Selepe[4], Cheryl Louw[5], Jenni Smit[6], Khatija Ahmed[7], Linda-Gail Bekker[8], Philip Kotze[9], Jared Baeten[1], Thesla Palanee-Phillips[2,3] for the ECHO Trial Consortium

[1]Gilead Sciences, Inc., Foster City, CA, USA; [2]Wits RHI, University of the Witwatersrand, Johannesburg, South Africa; [3]Department of Global Health, University of Washington, Seattle, Washington, United States of America; [4]Klerksdorp Clinical Research Centre, The Aurum Institute, Johannesburg, South Africa; [5]Department of Obstetrics and Gynaecology, Faculty of Health Sciences, University of the Witwatersrand, Durban, South Africa; [6]Wits MRU Department of Obstetrics and Gynaecology, University of the Witwatersrand, Durban, South Africa; [7]Setshaba Research Centre, Tshwane, South Africa; [8]University of Cape Town & Desmond Tutu HIV Centre, Cape Town, South Africa; [9]Qhakaza Mbokodo Research Clinic, Ladysmith, South Africa

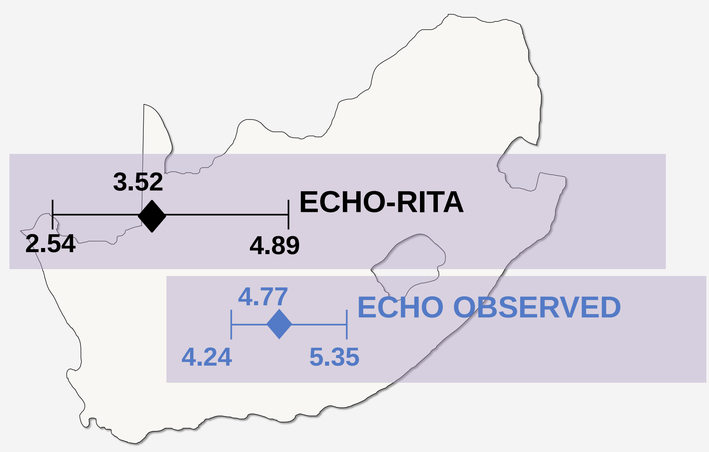
Key Findings

- The ECHO-recent infection testing algorithm (RITA) analysis showed that estimation of RITA-based HIV incidence among young women was similar to the observed incidence (3.52 vs 4.77 per 100 person years) (**Figure 1**)
  - Similar results were seen with varying RITA parameters (higher viral load [VL], cut-off and shorter time), indicating that the methodology is robust
- When comparing HIV incidence by age group and by study arm, there was good agreement between ECHO-RITA based estimations and observed incidences
- RITAs, using the Sedia® HIV-1 LAg-Avidity EIA recency assay, can be used to estimate background HIV incidence (bHIV) in clinical trials

Conclusions

- ECHO-RITA demonstrates that the Sedia® LAg-Avidity EIA recency assay and RITA accurately estimate HIV incidence in young women from South Africa with high access to antiretroviral therapy and predominantly subtype C HIV exposure
- This analysis also strongly supports use of the LAg-Avidity EIA recency assay and RITA to estimate bHIV in the counterfactual designs of next-generation HIV prevention trials, such as the ongoing Phase 3 studies of SC twice-yearly lenacapavir for PrEP (www.purposestudies.com)
- ECHO-RITA demonstrates proof of concept that Sedia® LAg-Avidity EIA and RITA bHIV incidence estimates provide similar results to prospectively observed bHIV

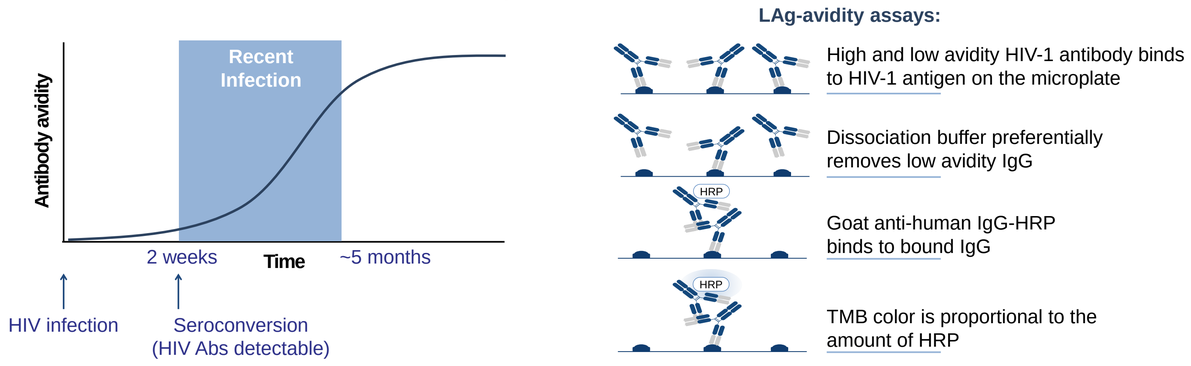
Figure 1. Mean ECHO-RITA and ECHO observed HIV incidences in South Africa per 100 person years, plotted with 95% confidence interval



Background

- Despite effective, daily, oral pre-exposure prophylaxis (PrEP) options being approved and included in routine care for HIV-1 prevention in most countries,[1] there is still a significant unmet clinical need
- Challenges exist within the current approaches to PrEP clinical trials:[2]
  - Due to the availability of effective PrEP, it is unethical to include a placebo-only group
  - Non-inferiority trials require increasingly impractical study sizes and are not possible for some populations (e.g., cisgender women)
- HIV-1 RITAs using recency assays are being employed in PrEP trials to estimate the counterfactual bHIV incidence, which is used as the intervention comparator[3]
  - Recency assays utilize the evolution of HIV antibody avidity following seroconversion to estimate recent infection (**Figure 2**), which provides the time component necessary for incidence rate estimation[4]
- ECHO (NCT02550067) was a longitudinal randomized clinical study among young African women comparing the incidence of HIV-1 infection in participants using different contraceptive methods
- The retrospectively performed ECHO-RITA analysis was a unique opportunity to compare RITA-based HIV incidence rate estimation to the prospectively observed HIV incidence[5–7]

Figure 2. Recency assays measure HIV antibody avidity through limiting-antigen (LAg) avidity assays; results indicate whether HIV infection occurred recently[4]

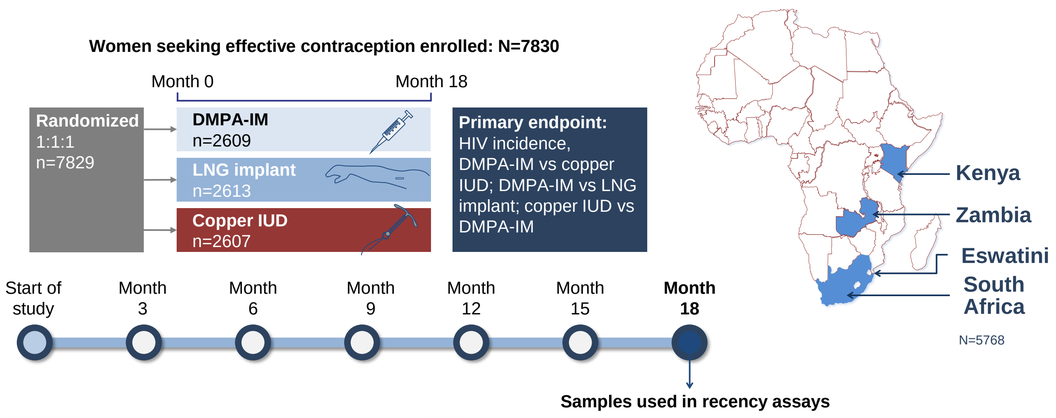


Antibody avidity was measured as an optical density (ODn) value
Abs, antibodies; HRP, horseradish peroxidase; IgG, immunoglobulin G; TMB, 3,3',5,5'-tetramethylbenzidine

ECHO trial

- ECHO assessed acquired HIV infection among women in four African countries between Dec 2015–Sep 2017 (**Figure 3**)[5–8]
- Eligible participants were non-pregnant, HIV-seronegative, aged 16–35 years

Figure 3. ECHO trial design, timeline, and participating countries[5–7]



DMPA-IM, depot medroxyprogesterone acetate intramuscular; LNG, levonorgestrel; IUD, intrauterine device

Objectives

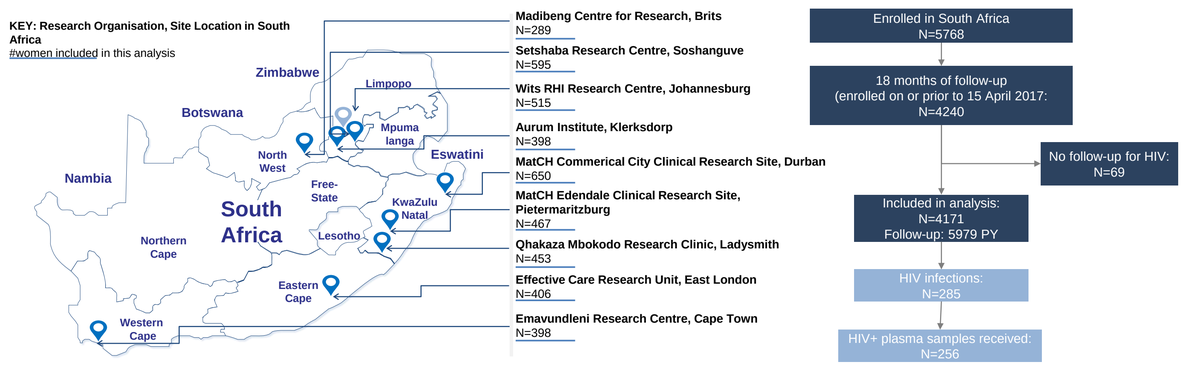
- The ECHO-RITA analysis was run to determine if the use of recency assays and RITAs could correctly estimate the bHIV compared to the established observed HIV incidence in the ECHO trial
- The following were estimated:
  - Overall HIV incidence
  - HIV incidence by age group
  - HIV incidence by trial arm

Methods

Analysis population

- In the ECHO-RITA analysis, participants were included who: 1) enrolled before 15 April 2017, 2) enrolled in one of nine South African ECHO trial sites, and 3) underwent the full 18 months of follow-up (**Figure 4**)
  - In South Africa, the most common HIV subtype is C[9]

Figure 4. Analysis of HIV incidence in women enrolled before 15 April 2017 across nine South African ECHO sites[8]



HIV+, HIV-positive; N, number of samples; PY, person years

Incidence calculations

- Recency assays and RITA analysis:
  - Recency assays were performed using the Sedia® HIV-1 Limiting Antigen Avidity Enzyme ImmunoAssay (LAg-Avidity EIA, parameters in **Table 1**[10]) with Month 18 visit samples, regardless of when HIV was acquired
  - The RITA used is consistent with the Forum for Collaborative Research Consensus Statement[4] and the WHO technical guidance[11] and uses the Kasanjee estimator[10] which includes a VL cutoff of 75 copies/mL
  - RITA-based HIV incidences were calculated using a mean duration of recency infection (MDRI) cut-off of 163 days (relative standard error [rSE] 8.3%), and a false-recency rate of 1.4% (rSE 100.3%)
- Observed HIV incidence was calculated at Month 18 using a formula based on Gao[12]
- ECHO-RITA-derived incidences were compared to observed HIV incidences

Table 1. RITA parameters[10]

Parameter	Value
Assay	Sedia® HIV-1 LAg-Avidity EIA
Normalized optical density threshold	1.5
VL threshold	75 copies/mL
Country	South Africa
HIV subtype	C
Time	2 years

In addition, two alternative parameters were used: Time = 1 year and VL threshold = 1000 copies/mL

- In addition, the number of samples at each visit correctly and incorrectly classified for recency was calculated
  - Classification was performed by examining when participants were last seen (how far this timepoint was from Month 18): recent or long-term infection was then defined, based on when participants had acquired HIV

Results

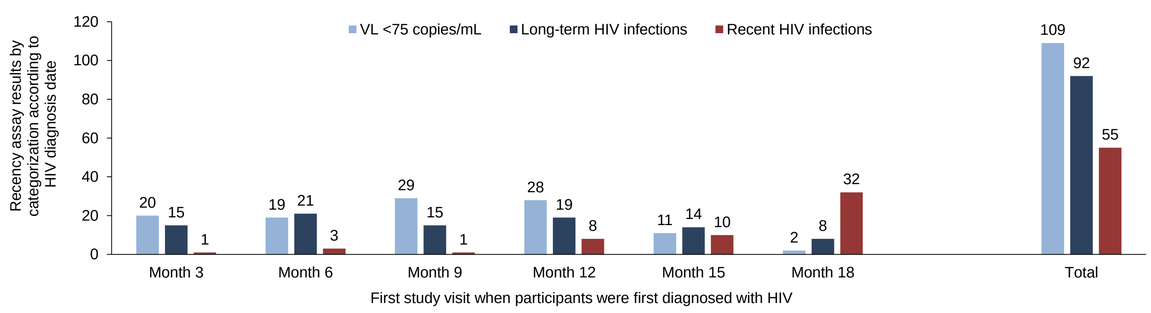
Sampling

- Among 5768 women in South Africa enrolled onto ECHO, 4171 were eligible for inclusion; 285 acquired HIV (**Figure 4**):
  - Of these, 256 had plasma samples from Month 18 available for recency assay testing
  - Across the study visits, the highest number of new HIV infections (55) was observed at Month 12
- Recency assay testing
  - Of the 256 HIV+ samples (**Figure 4**):
    - 109 samples had VL <75 copies/mL and were considered long-term infections
    - 147 samples with VL >75 copies/mL were analyzed using the LAg-Avidity EIA recency assay (in triplicate)

RITA sample categorization (Figure 5)

- Considering all available Month 18 samples, 55 (21.5%) were determined recent by the LAg-Avidity EIA
- Among non-recent Month 18 samples, 109 (42.6%) were considered non recent due to VL <75 copies/mL and 92 (35.9%) were determined non recent by the LAg-Avidity EIA
- Of the Month 18 samples, 36 (14.1%) had acquired HIV by Month 3; since these samples were collected ≥15 months post-HIV acquisition, they should be categorized as long term
  - 20 had a VL of <75 copies/mL, corresponding to long-term infection
  - 15 were categorized as long term by the LAg-Avidity EIA
  - 1 was incorrectly categorized as recent

Figure 5. Sample categorization by HIV diagnosis date, according to the Sedia® HIV-1 LAg-Avidity EIA

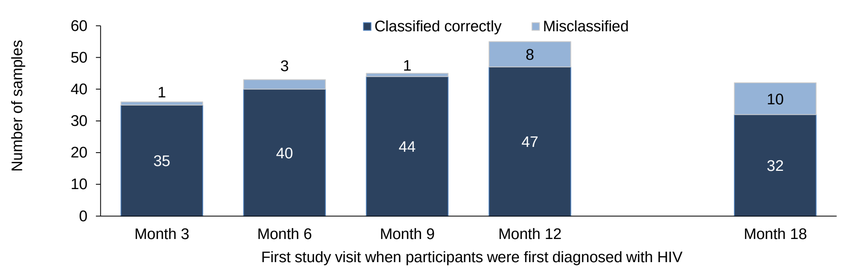


All recency assay results were conducted using Month 18 samples

RITA sample categorization

- The number of samples at each visit that were correctly and incorrectly classified for recency is shown in **Figure 6**
  - Most samples (81%) were correctly classified across visits in the 18-month period of follow-up
  - Month 15 participants could not be determined due to acquiring HIV 3–6 months previously and having an MDRI of 5 months

Figure 6. Number of samples classified correctly or misclassified for recency by visit



All recency assay results were conducted using Month 18 samples

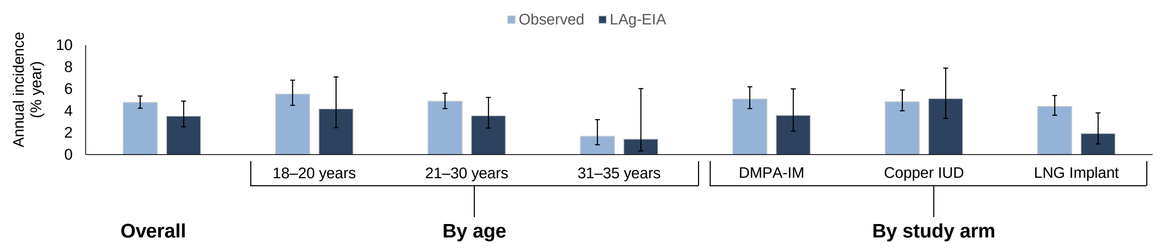
Overall HIV incidence

- ECHO-RITA-based HIV incidence estimates in South Africa were similar to observational data (**Figure 1**)
  - HIV incidence calculated based on RITA was 3.52/100 person years (PY) (95% CI, 2.54–4.89)
  - Observed HIV incidence was 4.77/100 PY (95% CI, 4.24–5.35)
- Estimated incidence based on differing RITA parameters:
  - Based on Time = 1 year: 3.71/100 PY (95% CI, 2.69–5.13)
  - Based on VL cut-off of 1000 copies/mL: 3.34/100 PY (95% CI, 2.23–4.88)

HIV incidence: subgroup analyses

- Based on ECHO-RITA and observational data, HIV incidence by age was highest in the 18–20 years group (**Figure 7**)
  - ECHO-RITA-based incidence in the 18–20 years age group was 4.18/100 PY (95% CI, 2.46–7.10)
- Based on ECHO-RITA, all three contraceptive method groups were found to be similar to the observed incidence, with overlapping confidence intervals (**Figure 7**)

Figure 7. HIV incidence in the ECHO trial in South Africa overall, by age range, and by study arm with RITA-based estimations (LAg-Avidity EIA)



References:

1. Murchu E, et al. *BMJ Open*. 2022;12(5):e048478; 2. Cutrell A, *HIV Clin Trials*. 2017;18:177–88; 3. Facente SN, et al. *JMIR Public Health Surveill*. 2022;8(3):e34410; 4. Parkin N, et al. *Clin Pharmacol Ther*. 2022;15:3083–94. 5. ClinicalTrials.gov 2023. https://clinicaltrials.gov/ct2/show/NCT02550067; 6. Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium. *Lancet*. 2019;394:303–13; 7. Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium. *Lancet.* 2019;394:303–13 (supplementary appendix); 8. Palanee-Phillips T, et al. *PLoS ONE*. 2022;17(6):e0269317; 9. https://www.aidsmap.com/about-hiv/hiv-1-subtypes; 10. Kassanjee R, et al. *AIDS.* 2016;30:2361–71; 11. WHO 2022 Technical Guidance https://www.who.int/publications/i/item/9789240064379. Accessed 14 July 2023. 12. Gao F, et al. *Stat Commun Infect Dis*. 2021;13(1):20200009.

Acknowledgments:

We extend our thanks to the participants, their families, and all participating investigators. This analysis was funded by Gilead Sciences, Inc. Medical writing support was provided by Ashfield MedComms, an Inizio company, Macclesfield, UK, funded by Gilead Sciences, Inc.

Please also see the following oral presentations for further details on the recency assay and RITA methodology for estimating counterfactual bHIV incidence in the PURPOSE program (ww.purposestudies.com):

1. Das M. *Experience with using recency assays to estimate HIV incidence in an HIV prevention trial.* SY05. 24 July 2023: 15:00–15:10, Plaza Ballroom/Channel
2. Das M. *HIV recency assay: lessons learned and challenges presented.* SAT050. 25 July 2023: 19:05–19:15, Plaza Ballroom/Channel 3

Disclosures: **S Cox, Y Shao, S Demirdjian, K Andreatta, A Nekkalapudi, C Carter, M Das, J Baeten:** Employees and shareholders of Gilead Sciences, Inc.. **H Rees, KB Heller, P Selepe, C Louw, J Smit, K Ahmed, P Kotze, and T Palansee-Phillips:** No conflicts of interest to declare. **LG Bekker:** received honoraria for advisories from Gilead Sciences, Inc., ViiV Healthcare, MSD (Pty) Ltd unrelated to this work.

International AIDS Society, 23–26 July 2023, Brisbane, Australia