4th Generation Rapid Tests Improve Detection of Acute Infection in MTN-003 (VOICE)

Edward Livant[1] , Amy Opest[2], Cliff Kelly[3], Rashika Maharaj[4], Natasha Samsunder[5], Lindiwe Nhlangulela[6], Patrick Karugaba[7], Jeanne Marrazzo[8], Zvavahera Mike Chirenje[9] and Urvi M. Parikh[2] on behalf of the VOICE Study Team

[1]Magee-Womens Research Institute, Pittsburgh, PA; [2]Univ of Pittsburgh, Pittsburgh, PA; [3]SCHARP, Seattle, WA; [4]Medical Research Council HIV Prevention Unit, Durban, South Africa; [5]CAPRISA, Durban, South Africa; [6]Aurum Institute, Klerksdorp, South Africa; [7]MU-JHU Research Collaboration, Kampala, Uganda; [8]Univ of Washington, Seattle, WA; [9]UZ-UCSF, Harare, Zimbabwe

Background/Objective

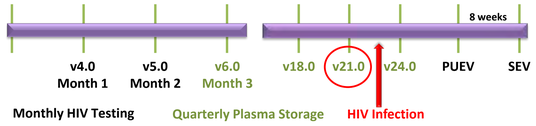
- The greatest risk of resistance to antiretrovirals (ARV) from pre-exposure prophylaxis (PrEP) is conferred by use during undetected acute infection.
- Early, accurate identification of HIV infection in HIV prevention trials is critical for protection of human subjects, data quality and study efficiency.

We evaluated pre-seroconversion plasma from VOICE to determine if 4th generation Ag/Ab rapid tests would have detected HIV infection earlier than the 3rd generation HIV rapid tests used in the trial.

Methods

- Phase 2B Safety and effectiveness study of tenofovir-based products for HIV prevention in women.
- 5029 participants from 15 sites in South Africa, Zimbabwe and Uganda

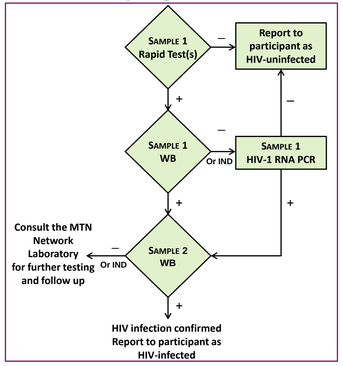
VOICE Visit and Plasma Storage Schedule



Pre-seroconversion plasma collected closest to the date of the first positive 3rd generation rapid detected at the site was selected for this study.

PUEV = product use end visit
SEV = study end visit

HIV Follow-Up Algorithm



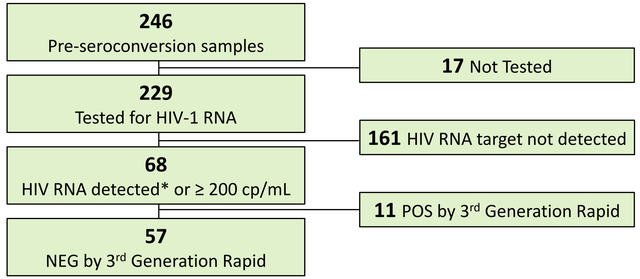
HIV Diagnostic Test Kits

Test	Used in VOICE	Under Evaluation
EIA	Bio-Rad GS HIV-1/2 +O	**Bio-Rad GS HIV Combo**
Rapid	1. Trinity Biotech Uni-Gold™ HIV test 2. OraQuick ADVANCE® Rapid HIV-1/2 3. Alere Determine™	**1. Alere™ Determine™ HIV-1/2 Ag/Ab Combo (FDA-Approved)** **2. Alere™ HIV Combo Rapid Test (CE-Marked)***
Confirmatory	Bio-Rad GS HIV Western Blot (WB)	Bio-Rad Multispot HIV-1/HIV-2 Bio-Rad Geenius HIV 1/2 Assay

4th Generation Antigen/Antibody (Ag/Ab) tests **IN BOLD**
*Note that this test is not the same as the CE-Marked Alere™ Determine ™ HIV-1/2 Ag/Ab Combo.

Results

Figure 1. Sample Consort Diagram



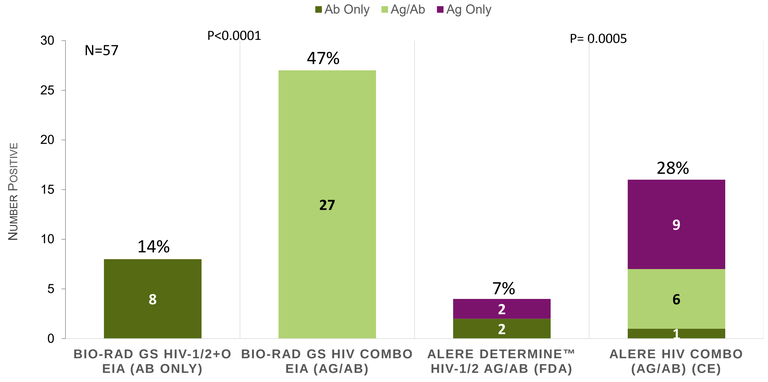
*7 samples had RNA result of target detected, <200 copies/mL

Table 1. Proportion of Pre-Seroconversion Samples with HIV-1 RNA Detected

Days Pre-Seroconversion	# Samples	# HIV RNA Detected
12-29 days	48	31 (65%)
30-59 days	98	31 (32%)
60-91 days	83	6 (7%)
TOTAL	**229**	**68 (30%)**

Assay Used: Roche Taqman with limit of detection at 200 copies/mL.

Figure 2. Proportion of RNA Positive/3rd Generation Rapid Negative Samples Detected as HIV Positive by 3rd and 4th Generation EIA and 4th Generation Rapid Tests



Specificity* 99.37% [96.52, 99.98] | 99.37% [96.52, 99.98] | 99.73% [95.50, 99.85] | 99.73% [95.50, 99.85]

*Based on 158 plasma samples with HIV RNA target not detected and 3rd generation rapid negative

- Bio-Rad GS HIV Combo (Ag/Ab EIA) detected 33% more early infections than Bio-Rad HIV-1/2+O (Ab only EIA) ($p < 0.0001$).
- Compared to 3rd Generation Rapid Tests Unigold and OraQuick:
  - FDA-approved Alere™ HIV-1/2 Ag/Ab Determine™ detected 7% of infections missed by current 3rd generation rapids.
  - CE-Marked Alere™ HIV Combo (Ag/Ab) detected 28% of infections missed by current 3rd generation rapids.

Table 3. Confirmatory Test Results

HIV Confirmatory Test	Bio-Rad GS HIV-1/2+O EIA (Ab only)	Bio-Rad GS HIV Combo EIA (Ag/Ab)	Alere Determine™ HIV-1/2 Ag/Ab (FDA-Approved)	Alere HIV Combo (CE-Marked)
Bio-Rad GS Western Blot	4 NEG, 4 IND	13 NEG, 14 IND	1 NEG, 3 IND	7 NEG, 9 IND
Bio-Rad Multispot	7 NEG, 1 POS	26 NEG, 1 POS	4 NEG	15 NEG, 1 POS
Bio-Rad Geenius	8 NEG	25 NEG, 2 HIV-2 IND	3 NEG, 1 HIV-2 IND	14 NEG, 2 HIV-2 IND

NEG = negative; POS = positive; IND = indeterminate

Conclusions

- In VOICE, 28% of infections missed by current 3rd gen rapid tests would have been identified with the use of CE-marked Alere™ HIV Combo (Figure 2).
- CE-marked Alere™ HIV Combo detected 21% more early infections than FDA-approved HIV-1/2 Ag/Ab Determine™ ($p = 0.0005$) (Figure 2).
- Bio-Rad Geenius, Multispot and Western blot were all insensitive (<10%) in confirming infections detected by 4th generation assays (Table 3).
- An improved diagnostic algorithm that includes 4th generation rapids with HIV RNA testing will be essential for efficiently identifying acutely infected individuals earlier.

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