NNRTI-Containing ART is Effective for Dapivirine Ring Breakthrough HIV-1 Infection

Sharon Riddler[1], Jennifer E. Balkus[2], John Mellors[1], Urvi Parikh[1], Carolyne Akello[3], Sufia Dadabhai[4], Felix Mhlanga[5], Colin O'Rourke[2], Jared Baeten[6], for the MTN-015 and MTN-020/ASPIRE Study Teams

[1]University of Pittsburgh, Pittsburgh, PA, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, [3]Makerere University-Johns Hopkins University Research Collaboration, Kampala, Uganda, [4]Johns Hopkins Bloomberg School of Public Health, Blantyre, Malawi, [5]University of Zimbabwe, Harare, Zimbabwe, [6]University of Washington, Seattle, WA

Background

- A vaginal ring containing the NNRTI, dapivirine (DPV) was found to be effective for prevention of HIV infection in two Phase 3, randomized, placebo-controlled clinical trials: MTN-020/ASPIRE and IPM-027/The Ring Study.
- Lockman et al. reported that a different NNRTI, single dose nevirapine (sdNVP) used for the prevention of mother-to-child transmission of HIV, was associated with ~3-fold increase in risk of virologic failure to first-line NNRTI-containing ART when ART was initiated within 6-12 months of receiving sdNVP. (*NEJM 2007;356:135-47*)
- NNRTI-containing regimens continue to be first-line ART in many regions of the world, thus it is critically important to assess outcomes in women with DPV exposure who become HIV infected and initiate ART.
- The MTN-020/ASPIRE trial enrolled 2,629 healthy HIV negative women at 15 sites in 4 African countries. Participants were randomized equally to use a monthly vaginal ring containing 25 mg dapivirine or a matching placebo ring. We assessed virologic failure and ART resistance following initiation of ART among women who acquired HIV infection during participation in ASPIRE.

Methods

- All ASPIRE participants with incident HIV during product use and with at least one CD4 cell count and HIV RNA (viral load) measurement were included in the analysis; the majority (77%) were enrolled into a longitudinal cohort follow up study (MTN-015).
- HIV seroconversion date was estimated as the mid-point between the last negative and first positive rapid HIV antibody test (performed monthly in ASPIRE).
- Virologic failure (VF) was defined as either
  - Lack of suppression of plasma HIV RNA to <200 copies/ml after 6 months of ART
  - Plasma HIV RNA rebound to ≥200 copies/ml at any time after suppression
- Standard genotypic resistance testing using an in-house assay (PR aa 1-99 and RT aa 1-333) was performed on plasma samples collected at VF.
- Descriptive statistics were used to summarize key factors. Categorical variables were compared by ASPIRE study arm using Fisher's exact test and time-to-event outcomes using the log-rank test.

Results

TABLE 1: Study population*

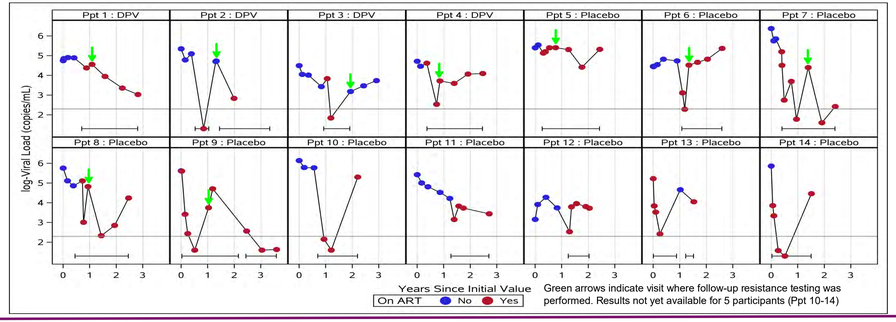
	All (N=158)	Placebo (N=93)	Dapivirine (N=65)
Age (years)	**23 (21, 27)**	25 (22, 27)	22 (20, 27)
Clade C virus**	**142/155 (92%)**	84/92 (91%)	58/63 (92%)
Initial HIV RNA (log_{10} copies/ml)	**4.6 (3.9, 5.2)**	4.6 (4.0, 5.2)	4.6 (3.6, 5.1)
Initial CD4 count (cells/mm^3)	**547 (429, 707)**	523 (396, 674)	601 (464, 793)
Median follow up (months)	**28.3**	29.0	26.7
Initiated ART	**87 (55%)**	54 (58%)	33 (51%)
At least 6 months FU on ART	**67/87 (77%)**	43/54 (80%)	24/33 (73%)
Virologic failure	**14/67 (21%)**	10/43 (23%)	4/24 (17%)

*Data presented as N(%) for categorical variables or median (interquartile range) for continuous variables
**3 women were missing data on HIV clade

TABLE 2: Resistance mutations at estimated seroconversion and virologic failure (VF)

Participant	ASPIRE Arm	Initial ART regimen	NNRTI mutations at seroconversion*	Mutations at VF
1	DPV	EFV/FTC/TDF	None	K103N
2	DPV	EFV/FTC/TDF	V108I/V, E138A	E138A
3	DPV	EFV/FTC/TDF	None	None
4	DPV	EFV/FTC/TDF	H221Y	V106M, Y181Y/C, H221Y
5	Placebo	EFV/FTC/TDF	None	None
6	Placebo	EFV/3TC/TDF	None	K103N
7	Placebo	NVP/3TC/d4T	None	G190G/A
8	Placebo	EFV/3TC/TDF	None	K103K/N
9	Placebo	NVP/3TC/d4T	None	K103N

*There was no significant between arm difference in the rate of NNRTI mutations at seroconversion in the MTN-020 trial (Baeten, et al. NEJM 2016)



Green arrows indicate visit where follow-up resistance testing was performed. Results not yet available for 5 participants (Ppt 10-14)

KEY FINDINGS:

- Of 168 participants with incident HIV infection observed in ASPIRE, 158 had at least one HIV RNA measurement and were included in the analysis (**Table 1**).
- 87/158 (55%) initiated ART (1 NNRTI + 2 NRTI) and 67 had ≥ 6 months follow-up on ART (median follow up on ART 15.7 months). Median time from HIV seroconversion to ART initiation was 11.7 months (IQR: 5.7, 21.1) and did not differ significantly between arms (Log-rank P=0.34).
- No significant difference was observed in the median time to virologic suppression among DPV and placebo participants (90 days vs 90 days; log-rank P=0.77)
- Virologic failure occurred in 14 participants with no significant difference between DPV and placebo recipients (17% vs 23%; Fisher's exact P=0.76). Among the 14 VF events, 8 were viral rebound and 6 never suppressed (**Figure**).
- 18/158 women with incident HIV infection on study product had one or more NNRTI resistance mutations, of which 10/18 initiated ART and had ≥6 months post-ART follow-up: 2/10 (20%) with NNRTI mutations vs. 12/57 (21%) with no NNRTI mutations had VF (Fisher's exact P>0.99)
- Genotypic resistance test results were available for 9/14 participants with VF (**Table 2**). NNRTI drug resistance mutations occurred in 7/9 overall; 6/7 were treatment-emergent. The most common mutation was K103N occurring in 4/9 participants.

Conclusions

- The use of the DPV ring in women acquiring HIV during the ASPIRE trial was not associated with significant differences in the virologic outcomes following initiation of NNRTI-containing ART
  - No significant difference in virologic response time or frequency of virologic failure among DPV recipients compared to placebo.
  - No evidence to suggest that the presence of NNRTI mutations at seroconversion impacted the rate of VF.
- These results provide reassurance that standard WHO-recommended ART regimens are effective in the setting of breakthrough HIV-1 infection in women who had received the DPV vaginal ring, although continued monitoring is warranted.

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