HIV Superinfection and the CAPRISA 004 Trial

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Background:

The CAPRISA 004 was a double-blind randomized clinical trial of 1% tenofovir (n=445 women) or placebo vaginal gel (n=444 women) applied before sex and another within 12 hours after sex based in South African medical clinics (1).

Sexually-active, non-pregnant HIV-uninfected women were enrolled and followed for 30 months.

The tenofovir vaginal gel reduced HIV acquisition by an estimated 39% overall, and by 54% in women with high gel adherence.

The HIV incidence in the tenofovir arm was found to be 5.6 per 100 women-years (38 out of 680.6 women-years) compared with 9.1 per 100 women-years (60 out of 660.7 women-years) in the placebo gel arm (incidence ratio = 0.61; P = 0.017).

Superinfection is defined when an individual is initially infected with an HIV-1 variant(s) and is subsequently infected with a new distinctly different variant.

A recent study from Rakai Health Sciences in Uganda found similar rate of HIV incidence (Incidence=1.15/100py) and the rate of HIV superinfection within their population (SI=1.44/100py)(2).

A study of high-risk female bar workers in Kenya found the rate of SI to be half of the rate of primary HIV infection(3).

Hypothesis:
The rate of HIV superinfection among seroconverters from the CAPRISA 004 trial was similar to the primary HIV incidence rate in the trial.

Methods:

96 women seroconverted during the CAPRISA 004 trial, the first time point and last time point before ART initiation were selected for analysis.

Viral RNA was extracted using the QIAmp Viral RNA Minikit.

Each sample was separately amplified for the p24 and gp41 regions using a RT-PCR reaction.

This first round product was used in a nested PCR reaction to amplify a specific 350-440 base pair region with unique primer barcodes designed for the 454 NGS platform.

Barcoded products were sent to the NIAID Core Facility in Hamilton, Montana for purification and pyrosequencing.

Definition of Superinfection Used For Analysis:

New phylogenetically distinct viral strain in second time point sample (either intra- or inter- subtype) that has a ample genetic distance from the first sample:

• p24 ≥0.59/ year or gp41 ≥0.98/ year

Results:

76 women were screened for superinfection (47 both regions, 12 gp41 & 17 p24 only).

All women were infected with subtype C except for one woman with subtype A.

Two women were found to be superinfected (2.6%) (Figure 1)

Viral load increased by >0.5 log during the window when superinfection occurred in both women (Figure 2).

Fig 1: HIV superinfection cases among CAPRISA 004 seroconverters. Phylogenetic tree of consensus gp41 viral sequences (10 reads) of a seroconversion (Blue) and a follow-up sample (Red), Distance is indicated for the tree by the scale at bottom of the tree, and samples are grouped with a selection of subtype reference sequences (black).

Fig 2: Viral loads from HIV SI cases. Viral load measurements for the two women (placebo arm, red; tenofovir arm, black) who became superinfected are shown, with the time frame in which SI occurred shown above.

<table>
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<tr>
<th>ID</th>
<th>Baseline Subtype</th>
<th>Baseline Reads</th>
<th>Baseline Con_Seq</th>
<th>SI Subtype</th>
<th>Follow-up Reads</th>
<th>Follow-up Con_Seq</th>
<th>Cons_Seq Strain</th>
<th>Baseline-Follow-up VL</th>
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<td>C</td>
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<td>C</td>
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</table>

Conclusions:

• Rate of superinfection within this population was found to be 1.5/100py (CI=0.7-7.1), which was significantly less than primary HIV incidence in the total CAPRISA 004 trial (IRR=0.20; p=0.003)

• These data differ than previous findings in the study in Rakai, Uganda, but agree with the findings from Kenya.

• A possible factor influencing these difference in findings is that CAPRISA 004 participants and Kenyan bar workers had very frequent follow-up visits (monthly) as opposed to annual visits in the Rakai cohort.

References:


