



HIV VACCINE TRIALS NETWORK

**HIV infected cases have lower pre-infection
Ad5-specific T cell response rates than
non-cases after Ad5/HIV vaccination
in the Step trial**

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Rationale

- Step trial volunteers with high baseline Ad5 nAb titers showed increased risk of infection in the vaccine relative to the placebo arm
- A potential mechanism for this relative increase in infection rates could be the increased availability of activated CD4⁺ T cells as targets for HIV
 - Ad5-specific memory cells would be reactivated by the Ad5 component of the vaccine in subjects with high Ad5 titers



Study population

- 20 HIV-infected cases infected after week 12
 - Those infected prior to week 30 (4 weeks after the 3rd vaccination) were studied at week 8 (4 weeks after the 2nd vaccination) ⇒ pre-HIV infection time points
- 286 HIV-uninfected participants at weeks 8 and 30 (“non-cases”)



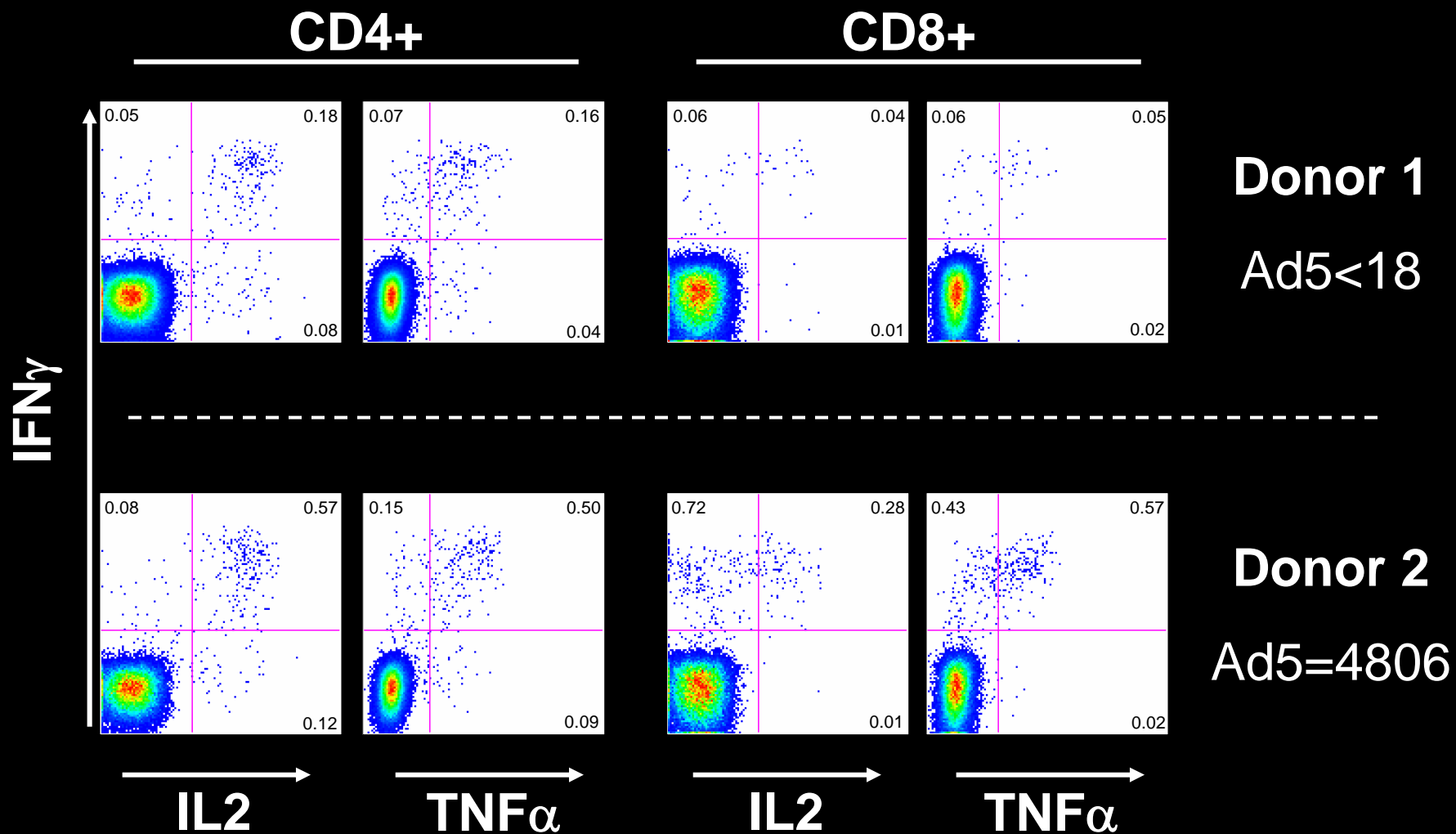
Methods

- PBMC were incubated with empty Ad5 vector (10,000 Ad5 particles per cell, VRC vector) overnight and examined for the presence of adenovirus-specific T cells secreting IFN- γ and/or IL-2 via intracellular cytokine staining
 - Possible detection of responses that are not Ad5-specific, but cross-reactive with other adenoviruses
- Samples were stratified by baseline Ad5 nAb titers into seronegative (≤ 18) or seropositive (> 18), and statistical tests were adjusted for region, circumcision status, and time of specimen collection.



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Representative Ad5 empty vector responses in two individuals



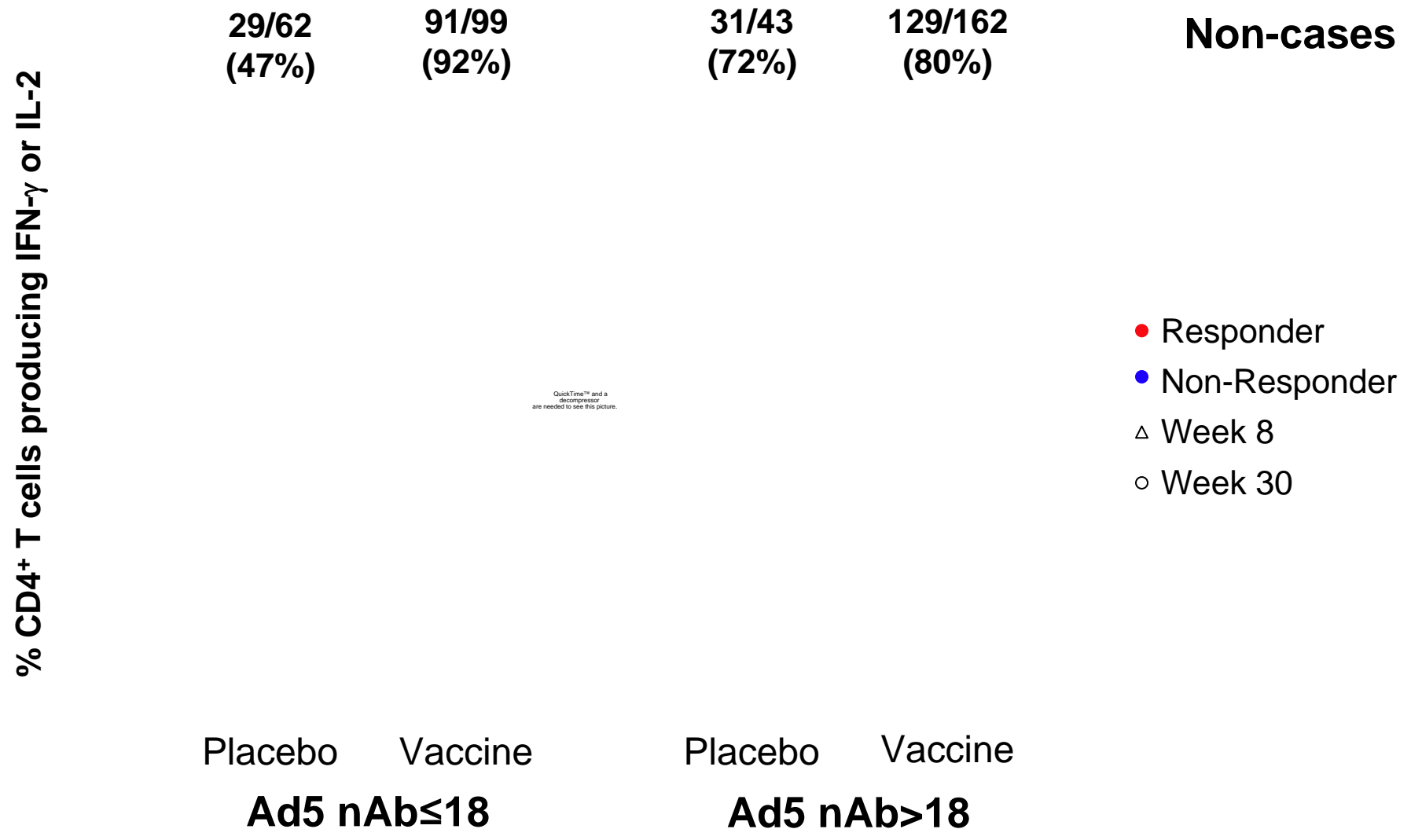


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T R I A L S N E T W O R K

**Comparison of Ad5-specific T cell responses
between vaccine and placebo recipients**

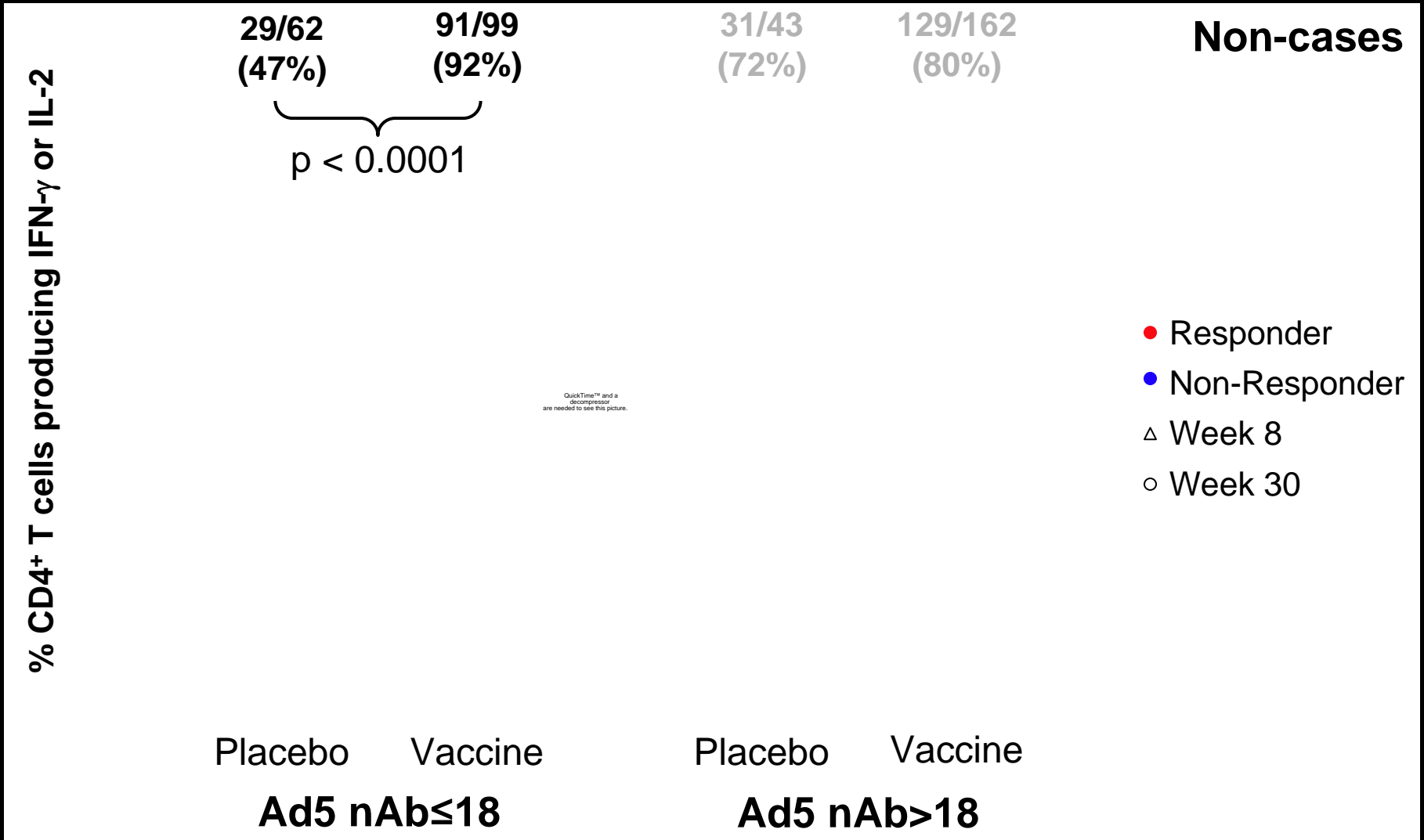


Vaccinees have higher Ad5-specific CD4+ T cell response rates than placebos



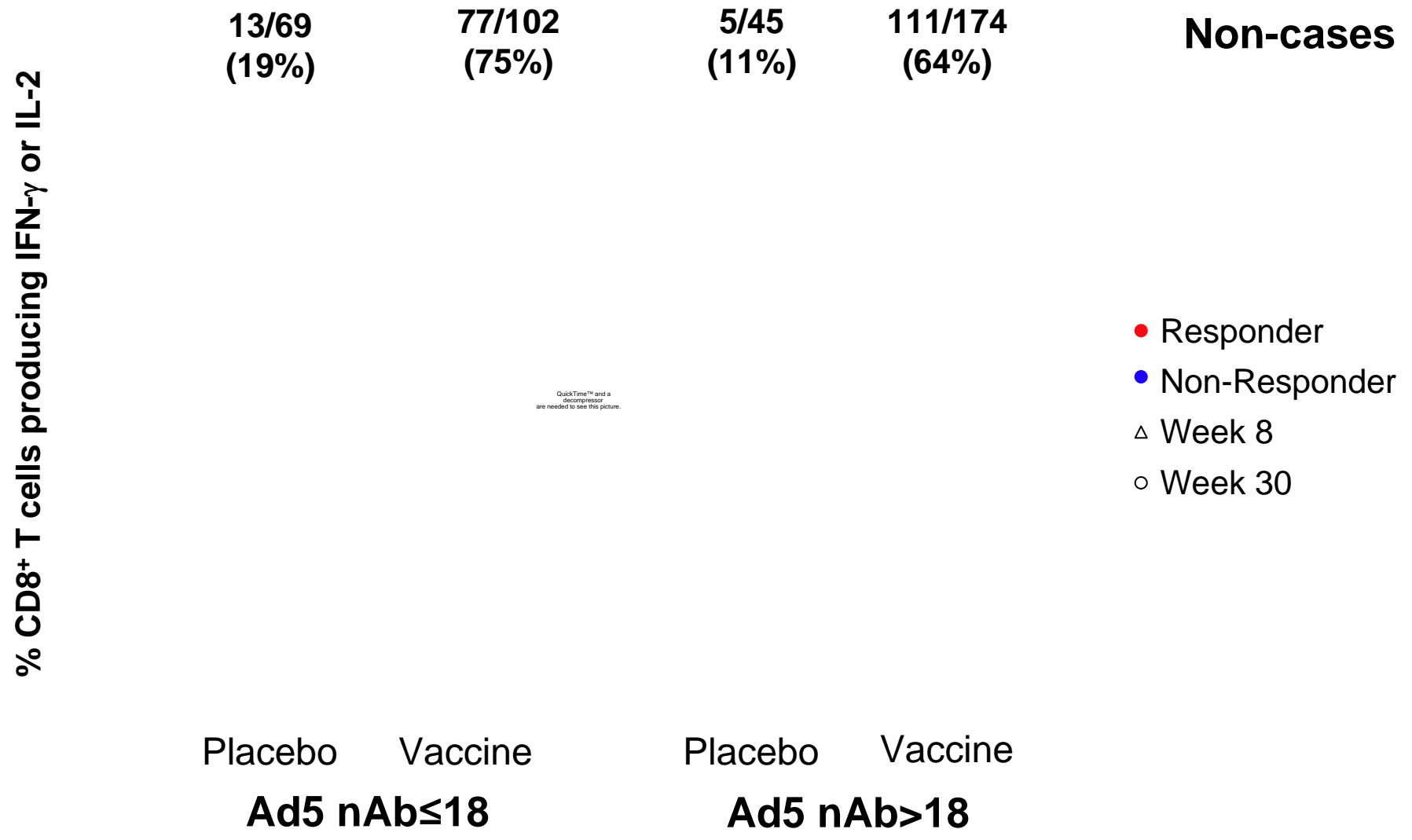


Vaccinees have higher Ad5-specific CD4+ T cell response rates than placebos



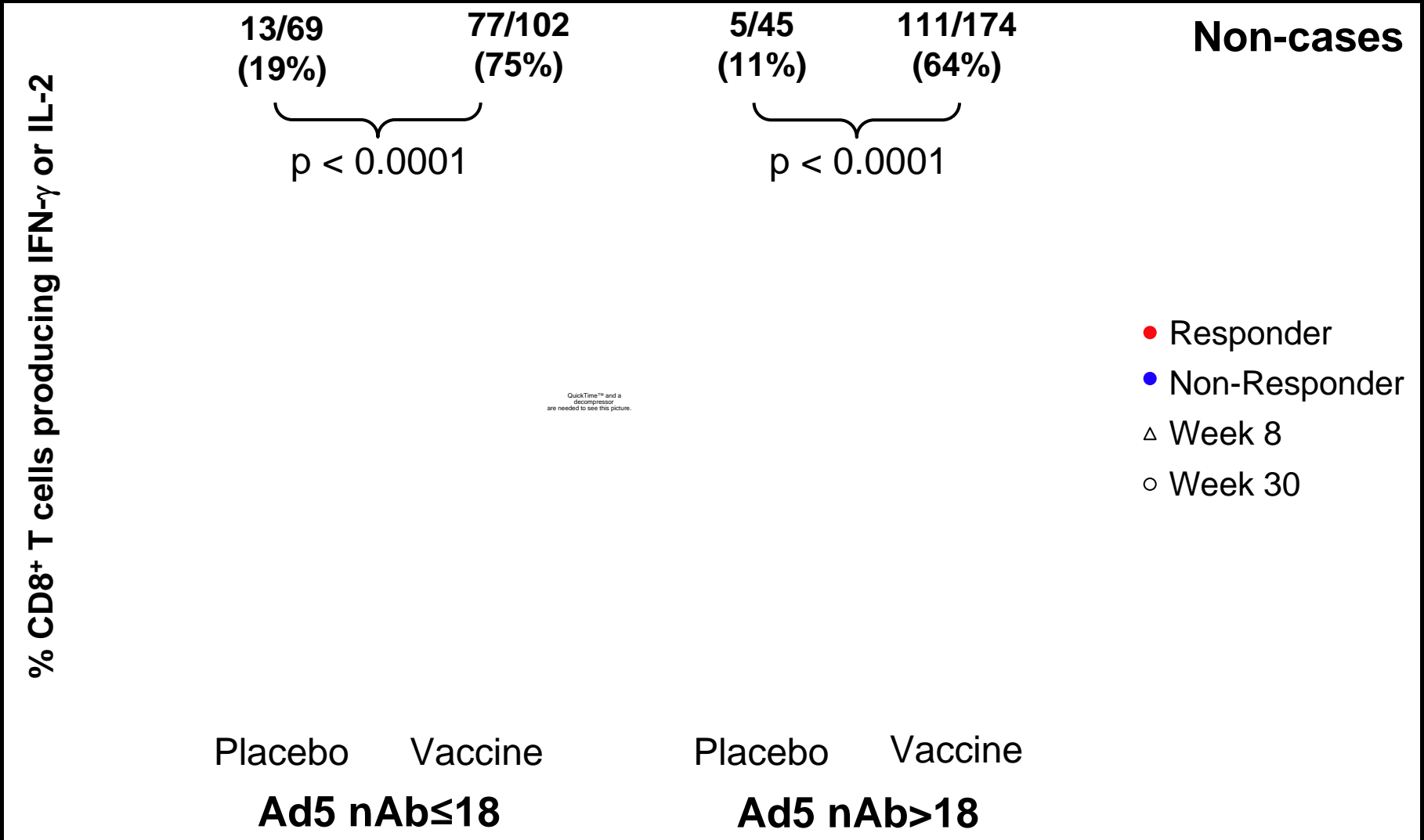


Vaccinees have higher Ad5-specific CD8+ T cell response rates than placebos





Vaccinees have higher Ad5-specific CD8⁺ T cell response rates than placebos





Summary

- In the Step trial, Ad5-specific CD4⁺ and CD8⁺ T cell responses were more frequently found in vaccinees than in placebo recipients
- Vaccinees also trended towards higher magnitudes of Ad5-specific CD4⁺ and CD8⁺ T cells
- Ad5-specific responses were more likely to be mediated by CD4⁺ T cells than CD8⁺ T cells, especially in placebo recipients



HIV VACCINE T R I A L S N E T W O R K

**Comparison of Ad5-specific T cell responses
between vaccinees that became HIV infected
(cases) and matched non-cases**



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Ad5-specific CD4⁺ T cell responses are more frequent in Ad5 seronegative than seropositive vaccinees

5/7
(71%)

7/13
(54%)

49/51
(96%)

50/68
(74%)

QuickTime™ and a
decompressor
are needed to see this picture.

- Responder
- Non-Responder
- △ Week 8
- Week 30



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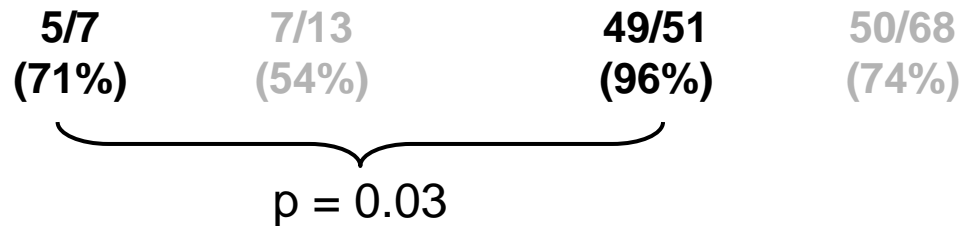
p = 0.005

QuickTime™ and a
decompressor
are needed to see this picture.

- Responder
- Non-Responder
- △ Week 8
- Week 30



Ad5-specific CD4⁺ T cell responses are more frequent in Ad5 seronegative non-cases than cases



QuickTime™ and a
decompressor
are needed to see this picture.

- Responder
- Non-Responder
- △ Week 8
- Week 30



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Ad5-specific CD8⁺ T cell responses are more frequent in Ad5 seronegative than seropositive vaccinees

3/6
(50%)

4/14
(29%)

42/53
(79%)

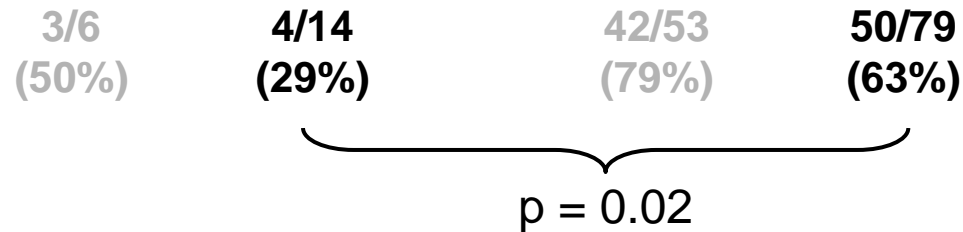
50/79
(63%)

QuickTime™ and a
decompressor
are needed to see this picture.

- Responder
- Non-Responder
- △ Week 8
- Week 30



Ad5-specific CD8⁺ T cell responses are more frequent in Ad5 seropositive non-cases than cases



QuickTime™ and a
decompressor
are needed to see this picture.

- Responder
- Non-Responder
- △ Week 8
- Week 30



Summary

- Ad5-specific CD4⁺ and CD8⁺ T cells were more frequently detected in Ad5 seronegative than seropositive vaccinees
- Unexpectedly, CD4⁺ T cell response rates in the blood were not higher in the cases than the non-cases, but few cases were available for analysis



Conclusions

- First insight into vector-specific cellular immune responses in vaccine and placebo recipients
 - Higher responses in vaccinees as expected
 - Immune response mostly CD4⁺ T cell mediated
- Lower Ad5-specific cellular immune responses in Ad5 seropositive vaccinees
 - No correlation with humoral immune response
 - Blunting of immune responses by pre-existing nAb preventing delivery of vector?



Conclusions cont'd

- No indication of higher Ad5-specific CD4⁺ T cell responses in HIV-infected cases
 - Numbers are small
 - Maybe homing of activated T cells to mucosa - additional studies looking at mucosal immune responses are necessary



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