Questions on the demonstration of systemic PreP efficacy

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On the design and interpretation of clinical trials

- **Are placebo controlled trials ethical?**
- **If not, is superiority over Truvada attainable?**
- **If not, can an M1 be justified (constancy of assumptions)?**
  - **If so, is the required sample size feasible?**
- **If M1 is not fully justified, can superiority over placebo still be inferred through the totality of evidence (including, e.g., STI rates, adherence monitoring, drug concentrations, viral drug resistance in case of infection)?**
- ***What are the alternatives if a sufficiently powered phase III study with HIV infection as endpoint is not feasible?***

Could acceptable PreP efficacy be inferred without large-scale clinical trials – and how would we get there?

- **Could NHP studies provide evidence of human PreP efficacy? Could a NHP-human bridge be constructed? What would be required for this?**
- **Can PK correlates of protection be established? If so, how? Which measurement matrix?**
- **To what extent can efficacy conclusions be extrapolated between drugs / drug combinations with the same MoA?**

  -To what extent do measurable differences in tissue distribution (e.g TDF versus TAF) matter?

(Continued)

- **Could it, for all potentially relevant MoA, be assumed that a therapeutic dose effective as an ARV regimen component would also be appropriate for effective PreP therapy (alone or with another drug)?**
- **Are real differences in PK/PD and efficacy between men and women anticipated?**
- **Could preclinical and human PK data in combination ever be translated into a reasonably accurate metric of protection?**
- ***Under what circumstances, if any, would subjects at risk, and their prescribers accept an inference of PreP efficacy without a formal demonstration in clinical trials?***