Transcutaneous Refillable Nanofluidic Implant for Constant Delivery of HIV PrEP

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Abstract
Antiretroviral drugs such as tenofovir alafenamide (TAF) and emtricitabine (FTC), are effective pre-exposure prophylaxis (PrEP) for HIV prevention. To address the issue of poor patient adherence, we developed a novel transcutaneously refillable nanochannel system (nDS) for the delivery of TAF and FTC. We hypothesized that the nDS implant could deliver sustained doses of HIV PrEP drugs, TAF and FTC, in non-human primates. We microfabricated silicon nanochannel membranes in compliance with FDA requirement for implantable devices. In this study, nDS was tailored for the controlled delivery of delivery of TAF and FTC and designed for transcutaneous refilling to extend treatment duration. PK studies were performed in three rhesus macaques with nDS subcutaneously inserted in the dorsum. The nDS implants demonstrated sustained release of both TAF and FTC for over 83 days, with transcutaneous refilling procedure performed on Day 70. PK data showed that nDS achieved sustained preventative levels of TFV-DP above 70 fmol/10^6 PBMCs over 83 days. FTC levels of approximately 1.5 pmol/10^6 PBMCs were sustained for 28 days followed by a gradual decrease due to drug depletion in the implant reservoir. Transcutaneous refilling proved successful with FTC levels restored to above 1.5 pmol/10^6 PBMCs. The nDS implants were well tolerated. Our results demonstrate the feasibility of the nDS approach as a solution to poor patient adherence to HIV PrEP.

Tissue and nDS membrane analysis

Figure 5. (A) nDS implants from pilot study in a rhesus macaque. (B) H&E histology of (B) normal skin, (C) skin adjacent to nDS-FTC and (D) nDS-TAF. (E) Scanning electron microscopy (SEM) image of nanochannel membrane retrieved from rhesus macaque in pilot study after 60 days of implantation.

Conclusions
- Nanochannel membrane-controlled drug release achieved sustained delivery of TAF and FTC for ~3 months.
- Successful transcutaneous refilling of drug reservoir was achieved in rhesus macaques.
- Compatible with HIV PrEP, target preventative TFV-DP levels were exceeded in PBMCs.
- FTC-TP did not reach preventative concentrations, so a study to increase release rate and drug concentration is currently being developed.
- Future studies with SHIV challenge (supported by NIH and Gilead) will be performed to examine the potential of nDS as a breakthrough delivery system to address poor patient compliance to HIV PrEP.

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