Introduction
At the end of 2019, 38 million people were living with human immunodeficiency virus (HIV), which is recognised by the World Health Organization as a major global health problem. Of these, 1.7 million were new diagnoses, three times higher than the UNAIDS 2020 target. Current HIV treatments are usually delivered orally or via intramuscular injection. This project involves formulating cationic nanosuspensions (NS’s) of two antiretroviral drugs, cabotegravir (CAB) and rilpivirine (RIL), into separate dissolving microneedle (MN) arrays which when applied to the skin offer a patient-friendly alternative to hypodermic needles for long acting delivery.

Materials and Methods
To increase drug loading and increase the efficiency of drug delivery, both RIL and CAB were formulated into nanocrystals via small scale wet bead milling with yttria stabilised zirconium beads employed as the milling media, as shown in Fig. 1 below, where energy was provided to the system with the use of a magnetic stir plate.

The formulations were developed with the use of Design-Expert experimental modelling software, Fig. 2, using RIL in the trials.

After 20 hours of milling the NS was recovered and analysis was conducted using a Brookhaven Nanobrook Omni. NS obtained were lyophilised with cryoprotectant to concentrate the drug and increase stability. MN arrays were formulated in a two-step process as shown in Fig. 3. Aqueous blends of polymer and lyophilised NS were produced in a SpeedMixer and an excess of this formulation was spotted onto the centre of silicon MN moulds (600 needles, 750 µm height, base width of 300 µm, 50 µm interspacing at the base). Once held at a pressure of 4.5 bar for a total of 10 minutes, the excess formulation was removed, and these were left to dry at room temperature for 20 hours. A second layer was then added as the baseplate, 300 mg of PVP 58 kDa 30% w/w.

Following removal from the moulds, MN were characterised using a light microscope. Drug content analysis was performed using HPLC-UV.

Results and Discussion
Prior to lyophilisation, RIL NC had a particle size of 163.13 ± 5.46 nm and a PDI of 0.109 ± 0.006 (n = 3). Particle size was retained during lyophilisation and zeta potential was determined to be +16.87 ± 0.53 mV (n = 3) as shown in Fig. 4a. CAB NC had a particle size of 194.79 ± 2.70 nm and a PDI of 0.129 ± 0.037 (n = 3). Particle size was again retained during lyophilisation and zeta potential was +17.29 ± 0.26 mV (n = 3) as shown in Fig. 4b. Both sets of MN arrays were well formed and had good mechanical strength on insertion into a previously described Parafilm M skin model. Each RIL MN array (Fig. 5a) was found to contain 2.47 ± 0.39 mg of drug while CAB MN (Fig. 5b) contained 3.09 ± 0.15 mg (n = 3).

Conclusion
NS of RIL and of CAB were successfully formulated with the desired characteristics via wet bead milling. These NS were lyophilised and incorporated into dissolving MN arrays which were well formed, had good mechanical strength and high drug loading. Further studies are needed to assess the in vitro release and delivery of the drug from these MN arrays.

References
1. Global Statistics – HIV.gov