UK-CAB 76: Meeting with ViiV Healthcare

Friday 12 February 2021

Meeting report

Present from ViiV:

Sylvia Nicholson - Policy Director
Andrew Murungi - UK Medical Director
Emilie Elliot - Cabotegravir Medical Director (Global)
Piotr Budnik - Prevention Medical Director (Global)

Contents

Summary

ViiV shared a lot of data about their studies.

ViiV showed results of two-drug regimens (2DRs) using their integrase inhibitor (INI) dolutegravir with lamivudine (DTG/3TC) compared with triple therapy (TT). All results seem to show that a 2DR is as safe and effective as TT, with possibly fewer adverse events, and the potential for fewer drug-drug interactions if treatment is ever needed for other health conditions.

ViiV have been developing long-acting drugs, using cabotegravir (CAB), also an INI. Initially this was a monthly intramuscular injection; now they are showing that a 2-monthly injectable is as effective and safe. Trials have been done using this both for treatment for HIV, but also as PrEP to prevent HIV. It has been very effective in trials for PrEP. There have been concerns raised about the length of time CAB stays in the body after discontinuation, with the fear that this could lead to the development of resistance. ViiV is working to gather more information about this, and wants to work with the community to minimise any risks. ViiV aim to price CAB-LA options for both treatment and PrEP so that they are accessible to all those who need them.

The concerns about weight gain with INIs were discussed. This is a complex area, but it does seem that INIs lead to more weight gain than other drug classes, particularly in women, and those of African origin. Switching from TDF to TAF is also associated with weight gain, though this may be due to TDF being weight suppressing rather than TAF causing weight gain. More studies are being done.

Most interesting was their view of the future, using novel drugs currently being evaluated in their pipeline. This could open the door to more acceptable long-acting options than intramuscular (IM) injections at clinic every 2 months. Self-administered monthly injections at home and 6-monthly IV infusions, or annual implants, at clinic are options being looked at, as well as 3-monthly IM injections.

1. Background

When we last met with ViiV (nearly 2 years ago?), there was a lot of concern about weight gain with integrase inhibitors (INIs). We were keen to get more information on this, as well as other matters. We asked some rather specific questions about their specific trials, as well as more general ones.

UK-CAB had sent questions in advance to ViiV. These questions, with ViiV's response, are discussed below.

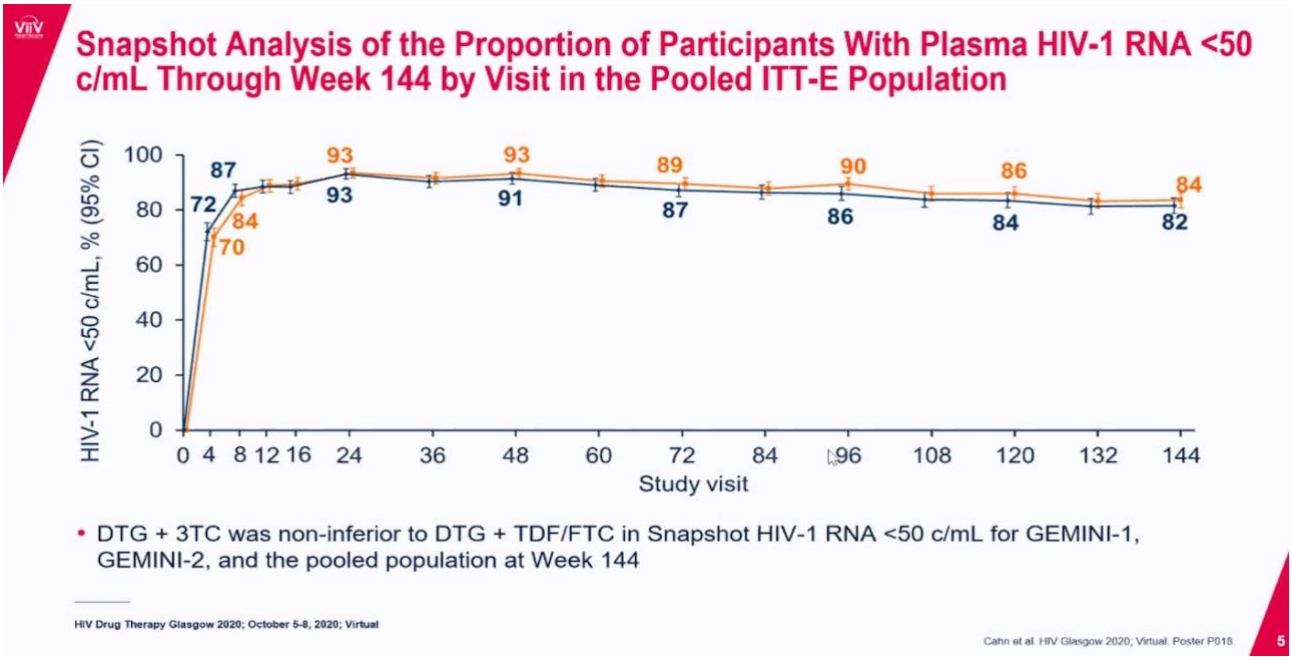
2. Meeting

a) HIV Treatment
b) Long-acting injectables for treatment
c) Long-acting injectables for PrEP
d) HIV trials
e) Weight gain
f) Pipeline

a) HIV Treatment

1. Please update us on the latest results from the GEMINI studies and the TANGO study, both of which compare 2 drug regimens (2DR) to triple therapy (TT), using dolutegravir/lamivudine. Some concerns have been raised about the development of resistance in 2 drug regimens. There have also been concerns about the risk of increased levels of inflammation with 2DR. What is your response to this, and what are your plans in this area?

GEMINI-1 and GEMINI-2 compared a 2 drug regimen (2DR) dolutegravir/lamivudine (DTG/3TC) with dolutegravir triple therapy (TT) in treatment-naïve adults.



The results show that there is no significant difference between the 2DR and TT arms in the study. A question was asked about what looks like a decline in the percentage of undetectable participants in both arms, from about 93% at week 24, to 82-84% at week 144. This was put down to people dropping out of follow-up on the trial, rather than any decline in the effectiveness of he ART. The high rate of drop-out was put down to the impact of Covid, preventing people from attending trial monitoring sessions. At week 144, about 15% of participants (so about 100 in each arm) had discontinued, mostly for "loss to follow-up".

With regard to confirmed virological withdrawal (CVWs), and whether these gave rise to any evidence of resistance, it was pointed out that there were few instances of these in either arm (1-2%), and none of these had any treatment-emergent resistance mutations.

It was also pointed out that there were fewer drug-related Adverse Events (AEs) on the 2DR arm compared to the TT arm (20% vs 27%). But there were few Ads leading to withdrawal from the study (4-5%in each arm). There were very few CVWs (<1% at week 96, all in the TT arm), and no resistance mutations were observed.

TANGO is a similar study comparing 2DR to TT, but on patients already on treatment who switch from TT to 2DR. Again, there was a degree of drop-out due to covid. When this was taken into account, there was no statistical difference between the 2DR and TT arms, both with high efficacy. There were slightly more drug-related AEs in the 2DR arm (6% vs 2%). This was put down to AEs related to switching regimens, which is commonly seen.

With regard to inflammation, it was pointed out that inflammation cannot be measures in tissues in routine practice. But there may be some products that can be measured in clinical practice and have the potential to be used as markers of inflammation. However, there is no stable, reproducible and reliable biomarker identified to date. Some biomarkers were looked at (D-dimer and IL-6), but changes to week 48 were small and inconclusive. The concern is that a 2DR may not penetrate the HIV reservoirs in the body (such as in the CSF, genital tract or gut) as well as TT. There is some limited data which suggests 2DR are present in the CSF and genital tract, but the data is limited, and further studies are needed to address this issue more conclusively.

b) Long-acting Injectables for Treatment

2. Please update us with the latest results from both the ATLAS and FLAIR studies, using long-acting injectable cabotegravir/rilpivirine (CAB/RPV). ATLAS-2M looked at giving the injections every two months. There were more viral failures here, and more development of resistance, both to rilpivirine and cabotegravir. How concerned should we be about this? Are you doing more studies in this area?

The FLAIR and ATLAS trials looked at the use of monthly injections of long-acting cabotegravir/rilpivirine (CAB/RPV) compared with a TT regimen containing dolutegravir (DTG). There was no difference between the two., and no CVWs between weeks 48 and 96. Most participants on ATLAS continued on to ATLAS-2M, which compared monthly CAB/RPV injections with injections every 2 months. 2 monthly dosing was found to be as effective as 1-monthly dosing. But there were slight virological failures reported in the 2-monthly arm than in the 1-monthly arm (8 cases vs 2 cases), though the number of resistance mutations was very low. An analysis has been done to see what factors might be predictive of virological failure. Although 4 variables were identified as being associated with increased odds of virological failure, no single factor was predictive of failure. But having 2 baseline factors had a slightly increased risk. However, it was uncommon to see this in individual participants (3%). The baseline factors that gave rise to this increase risk are:

- HIV-subtype A6/A1 (uncommon outside of Russia)
- BMI >30 kg/m^2
- RPV resistance-associated mutations

Further studies are being done: SOLAR and CARISEL. SOLAR is looking at CAB/RPV injectables vs Biktarvy. Biktarvy is a Gilead combination of three separate antiretroviral drugs in one pill, combining an INI, bictegravir (BIC), with emtricibatine (FTC) and tenofovir alafenamide (TAF). SOLAR is also designed to look at weight gain and metabolic issues. CARISEL is looking at 2-monthly injections in the clinical setting. Results may be reported late 2021.

c) Long-acting Injectables for PrEP

3. With long-acting injectables, there is concern about the "tail", especially when being used for PrEP. When injections are discontinued, the drug remains in the body, at declining levels, for some time. This "tail" of active but declining drug in the body may not be protective. If drug levels insufficient to protect against HIV linger, and an individual becomes infected, the risk of developing drug resistant HIV is a worry but the actual risk of resistance is not clear. HPTN 083 trial participants are given daily oral TDF/FTC to "cover the tail" for 48 weeks after they stop injections, if they consider themselves to be at risk. Understanding the clinical relevance of the tail—what it means for resistance, drug-drug interactions, fertility, pregnancy and breastfeeding is essential. It will also be critical to understand the durability of self-assessments of risk—when a person stops injections and decides he or she does not need additional oral PrEP, does that align with their actual risk over the next 48 weeks in which the tail appears to persist. What results or information do you have from HPTN 083/HPTN 084 with regard to this issue? Are you doing any further qualitative studies in this area? How will you collect information on people who stop injectable treatment?

This is more of a concern for when CB LA is used for PrEP. CAB LA concentrations can persist for a year or longer following discontinuation. But the risk of developing HIV resistance on acquiring HIV after the final dose of CAB LA is still to be fully understood.

So, if someone is using CAB LA injectables for PrEP, what if they do not come back for their routine injection on time? Results from the HPTN studies show good adherence for injection visits. ViiV said: "But it is vital that this form of PrEP is given to select individuals who understand the importance of adhering to injection visits as long as there is a need for PrEP". In both HPTN083 and HPTN084, there were low levels of seroconversions in the CAB arms; the resistance profile of those who seroconverted is still pending. These trials are now open-label, but will continue. The following will be measured:

- Drug concentrations of each PrEP agent at the time of detection of HIV-1 infection
  - For CAB, PK profiles since inception to suppression
  - For TDF/FTC, TFV plasma and TFV-DP from peri-infection detection
- Resistance profiles of HIV acquired after exposure
  - At first detection
  - Over time, until suppression on ART

Measuring TDF in the blood only may not accurately reflect adherence, as it detects only recent use and is susceptible to "white-coat" effects, when individuals take a dose before a visit to appear adherent. TFV-DP is the active metabolite tenofovir-diphosphate. TFV-DP accumulates in blood cells in a dose-proportional manner (Anderson et al., 2017) and is a marker of cumulative use over the prior month. As a biomarker, TFV-DP is increasingly being used to assess adherence in research.

Several other studies will add to this data and address key questions that are important for the successful implementation of PrEP using CAB-LA. These include:

- safety, tolerability and acceptability studies
  - In adolescent US males (HPTN 083-01) - recruiting
  - In adolescent African females (HTPN 084-01) - pending protocol
- Studies to evaluate CAB in pregnancy and lactating women - under discussion

There is a need for ViiV and the community to work together, to manage any risks.

4. Cabotegravir/rilpivirine long-acting is now approved in the EU. How will you be marketing and pricing this - as first-line ART for everyone? Or for a limited market - and if so, who and why?

CAB-LA (2 monthly) is currently being assessed by NICE in the UK for treatment. This is the first time that NICE is involved in HIV treatment. ViiV expressed the view that NICE did not well understand HIV, and urged the UK-CAB to make their views about CAB-LA injectables clearly and strongly known to NICE. ViiV said that they could not discuss pricing, but reminded us that the NHS negotiates a list price (which is public), which does not always reflect the actual price (which is confidential). UK-CAB urged ViiV to price the product so that it would be accessible to all those who needed it. ViiV suggested that the price would be set reflecting the current Standard of Care, so it would be competitive.

It was noted that using CAB-LA 2-monthly injectables would involve 6 clinic visits per year for intra-muscular injections. This would (presumably) be in addition to seeing the HIV consultant regularly - this is now typically every 6 months, though for patients who are stable on ART, this may be less frequent (9-monthly or even annually). This would result in extra cost for the NHS, which in some way needs to be reflected in the way CAB-LA is priced.

5. You presented data about fostemsavir (BRIGHTE study) recently. This will be very important for those who are heavily treatment-experienced (or have multiple drug resistances). This is now approved in the US. How will you be pricing this? In the UK, high pricing for a limited market might easily lead to it not being approved in the UK, which would be a shame.

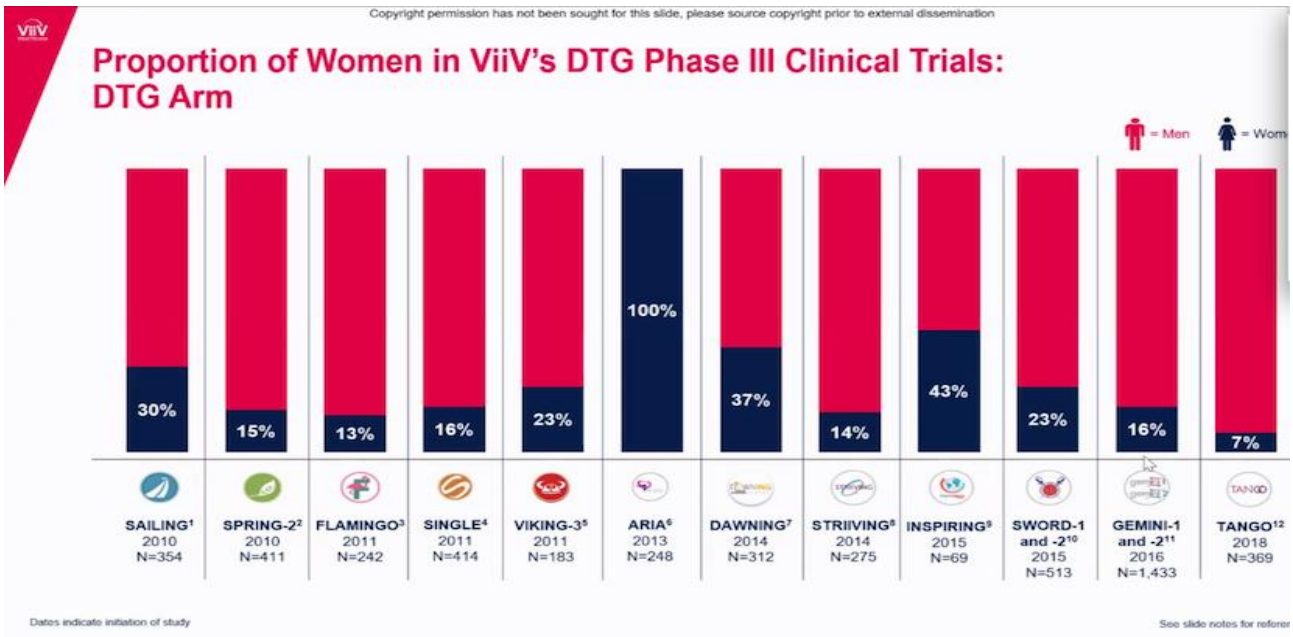
NHS England is currently evaluating this as an option for people with few remaining treatment options. ViiV's aim is to make it accessible to those who need it, but couldn't comment specifically on how it would be priced.

d) HIV trials

6. Clinical trials: please provide an overview of key current clinical trials and also how you reflect the community in trial populations, in terms of ethnicity, gender and age. We are encouraged to see the results of the HTPN 084 study (using cabotegravir LA as PrEP) in women. What is the current participation of women in your other clinical trials?

ViiV's ambition (as expressed by Kim Smith, ViiV's R&D head) is to have at least 25% women in trials going forward. UK-CAB suggested that this seems a low figure. ViiV replied that they were taking "baby steps", but the aim was to go beyond 24% progressively. ViiV noted that they had set up a task force to look at how better to recruit more women into their trials.

See diagram below.

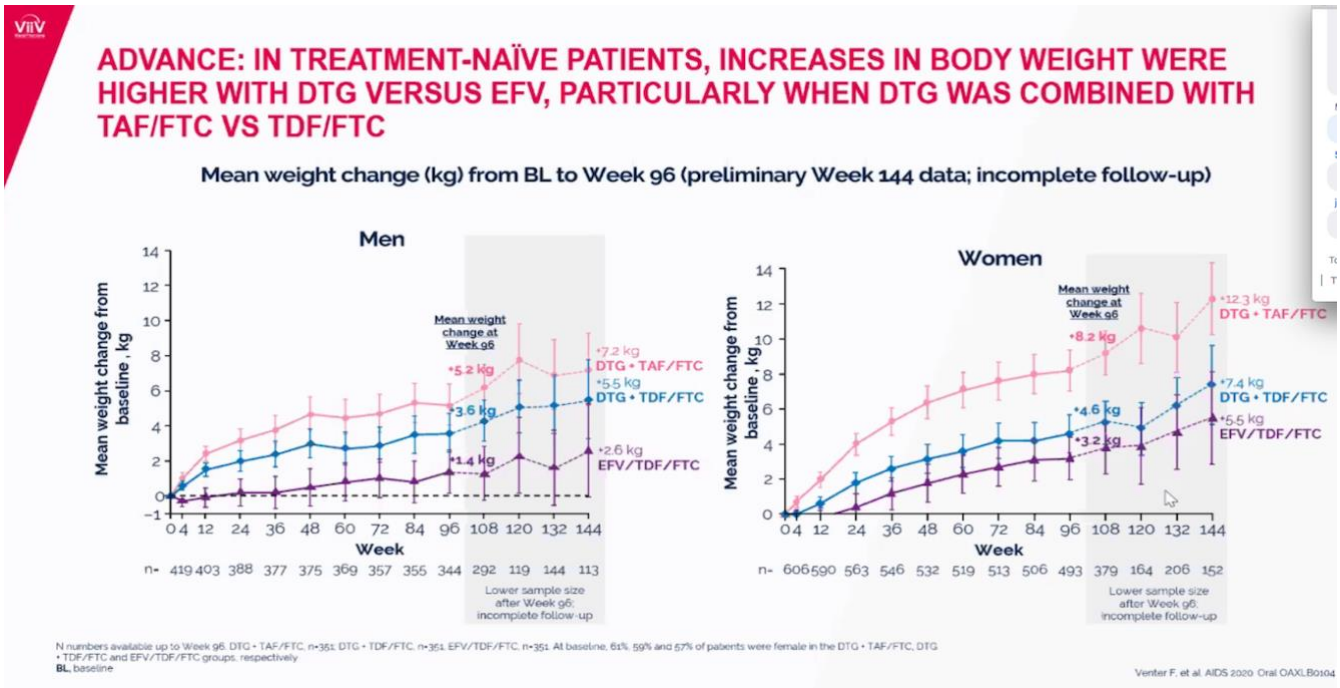


Weight Gain

7. There has been a lot of discussion and concern about weight gain associated with ART, and with INSTIs in particular. Please update us on the latest results from your ADVANCE study. Is thre any evidence to suggest the weight gain levels off? Or does weight gain continue to rise? The ADVANCE study is in Africa., and the biggest weight gain is in women there. Do you see similar effects in women of African origin in other countries such as the US or UK? Do you have any further insights into what cause the weight gain, or what sort of weight gain it is - there was a suggestion at the last meeting with ViiV that at least some of the weight gained was as muscle mass rather than fat? Do have any data on this?

The ADVANCE trial has 1053 participants, and has three arms:

- Dolutegravir with TAF/FTC
- Dolutegravir with TDF/FTC
- Efavirenz with TDF



There is data for week 144, and more data is expected later this year. Smaller studies had suggested that weight gain seemed to level off. However, the week 144 data from ADVANCE seems to suggest this is not the case: see diagram above.

It was pointed out that earlier studies (and ADVANCE?) were not specifically set up to look at weight gain, and there are many confounding issues. Changes in body composition to week 96 have been reported. These show that most of the weight gain, particularly in women, is as limb or trunk fat rather than lean body mass.

ViiV suggested that in ADVANCE, the weight difference between efavirenz and dolutegravir may be driven by impaired weight gain in people likely to have high efavirenz concentrations (such as women of African origin). ViiV suggested that a genotype (CYP2B6) may mutate to give slower metabolisation of efavirenz, leading to higher concentrations. Those with these slow metabolisers gained more weight when switching away from efavirenz. They also suggested that TDF suppress weight gain, so switching to TAF results in weight gain. And they pointed to weight gain associated with a return to health for people diagnosed with HIV who may be ill. They said it was a complex area, and it was difficult to tease out the impact of specific HIV drugs.

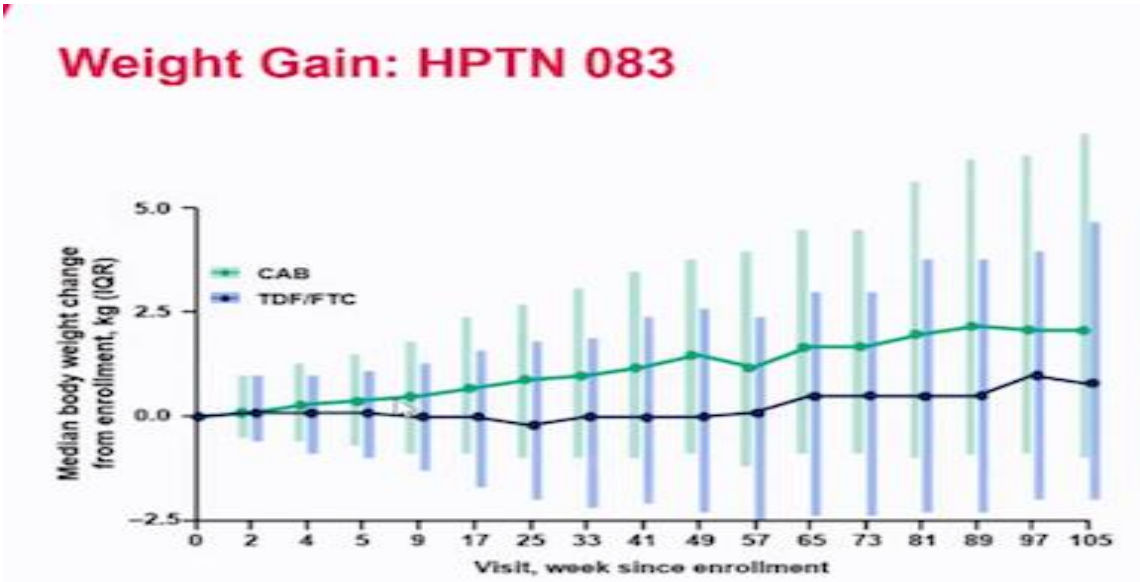
Nonetheless, cohort data (rather than trial data) does suggest that there are differences in weight gain seen between different drug classes, and integrase inhibitors do seem to be associated with greater weight gain than to ther classes.

ViiV is planning a trial to look specifically at metabolic syndrome. The trial, SOLAR, is a phase III trial looking at the efficacy, safety and tolerability of switching to CAB-LA (2-monthly) from a Biktarvy regimen. But it will also have specific objectives to evaluate changes in metabolic syndrome, and insulin resistance, and should give more information about what might be driving weight gain.

8. Will long-acting injectable therapy be associated with similar amounts of weight gain?

ViiV presented data from HPTN 077, which suggested that their CAB used for PrEP was not associated with significantly greater weight gain than placebo in HIV-negative individuals.

They also looked at data from HPTN 083. This is a much bigger trial, and here, there was a slight difference in weight gain between those receiving CAB as PrEP, and those receiving TDF/FTC.



What is perhaps more striking (though it was not commented on during the meeting) is the large range seen in both arms, as indicated by the vertical bars on the data points. Even though the mean weight gain at week 105 was about 1.3 kg for the CAB arm, it could also be well above 5 kg for some.

9.The HPTN 084 study showed good results for PrEP in women in Africa using long-acting cabotegravir. You have said this will be made affordable in Africa. Will it also be affordable in the EU/UK? How will you price it?

ViiV said pricing plans for CAB-LA used as pPrEP were not yet in place, but said again that the intent was to make it accessible for those who need it.

e) Pipeline

10. A number of questions were pulled together and addressed here:

- ***Rilpivirine LA requires cold chain distribution. Are you looking at other products to partner with cabotegravir?***
- ***Are you developing any long-acting injectables that last longer than 2 months?***
- ***Are you considering implants for HIV treatment?***
- ***Please update us on long-acting options for PrEP - oral; injectable; implant?***
- ***Please tell us about your maturation inhibitor (GSK3640254). Do you have any proof of concept dosing data yet? What are your plans for this drug? Do you have any others in this class?***
- ***Do you have any further data on combinectin?***
- ***You have an exclusive licence to develop some monoclonal antibodies such as N6LS. What are your results to date, and what are your plans in this area?***
- ***Are you developing any other new classes of ARV?***

ViiV highlighted their "Looking to the Future" objectives:

- Less frequent dosing and long-acting drugs
- Chemical entities vs biologics
- Home vs clinic administration
- Same vs mixed modality/administration interval

Currently, LA injectables using CAB are intra-muscular (IM). This needs to be done in clinic. A subcutaneous (SC) injection could be self-administered at home. The options being investigated are:

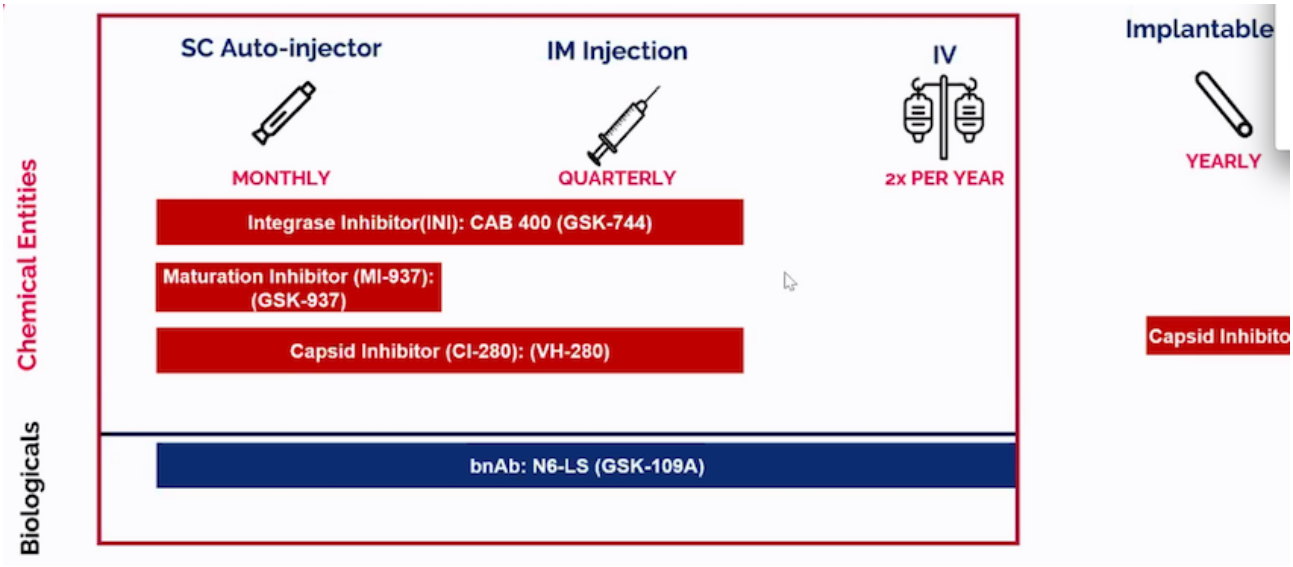
- Self-administration
  - One device, one SC injection, two co-formulated drugs Q1M (once a month)
  - One device, 2 SC injections Q1M
- Clinic administration
  - Two devices, 2 IM injections Q3M (every 3 months)
  - 1 or 2 15 minute intravenous (IV) infusions Q6M (every 6 months)

The options that are being prioritised are:

- Chemical entities
  - Integrase Inhibitor (INI): CAB 400mg for SC QM; IM Q3M
  - Maturation Inhibitor (MI): MI-937 for SC Q1M
  - Capsid Inhibitor (CI): CI-280 for SC QM; IM Q3M
  - Capsid Inhibitor: not named for implantable annually
  -

- Biologicals
  - bnAb: N6-LS for SC Q1M; IM Q3M; IV Q6M

These need to be made as combinations for a LA 2DR regimen.



This raises a number of new (and interesting) options for the future:

- 3-monthly IM at clinic
- Monthly SC at home
- 6-monthly IV infusion at clinic
- Annual implantable at clinic

All of these are at an early stage of development, but all seem more attractive than the current LA option, particularly the idea of self-administered SC injections at home, 6-monthly (15 minute) IV infusions, or annual implants.

UK-CAB Participants

	Name	Organisation	Destination
1	Alastair Hudson	East Midlands Sexual Health/ HIV Scotland	Edinburgh
2	Alex Sparrowhawk	UK-CAB SG/THT	Manchester
3	Ant Babajee	Positively UK	London
4	Ben Cromarty	Yorkshire Mesmac	Northallerton
5	Colin Stewart	Personal	London
6	David Williams	Personal	London
7	Husseina Hamza	Red Ribbon/Living Well	London
8	James Cole	STOPAIDS	London
9	James Dunworth	HIV i-Base	London
10	Jeff Ukiri	BHA For Equality	Manchester
11	Jo Josh	UK-CAB SG, Sophia Forum, BHIVA	London
12	Jon Bromberger	Positively UK	London
13	Kevin Snell	Terrence Higgins Trust Scotland	Glasgow
14	Mel Rattue	Mindful Herts	Watford
15	Memory Sachikonye	UK-CAB	London
16	Paul Clift	Personal	London
17	Richard	Switchboard / Positively UK	London
18	Rupert William Jones	Skyline	Leeds
19	Simon Collins	HIV i-Base	London
20	Suzanne Thompson	HIV i-Base	London
21	Wezi Thamm	Personal	London
22	William Edgill	Personal	London