UK-CAB 75: Meeting report
Meeting with Gilead Sciences
Wednesday 25 November 2020

Zoom virtual meeting

Present from Gilead:

1. Sylvia Alfred - Director Corporate Giving - ACE region (Australia Canada and Europe)
2. Felipe Rogato - Senior Director - Medical Affairs – HIV
3. William McCully - Associate Director, Medical Project Management, COVID-19

The meeting introduced by Sylvia Alfred, then was largely run by Felipe Rogato on HIV, with William McCully on COVID-19.

Contents

Summary

Gilead shared a lot of data about their studies. This shows how ABPI (Association of British pharmaceutical industries) regulations can be differently interpreted by different companies. The **ABPI** Code sets standards relating to the provision of information about prescription-only medicines to the public and patients, and pharmaceutical companies' relationships with patient organisations. But individual companies may interpret these differently.

Gilead discussed their view of two-drug combinations compared with triple therapy. At present, they favour triple therapy. Gilead have spent a lot of time showing the effectiveness of elvitegravir, in combination with other drugs. Elvitegravir needs cobicistat as a booster, which some in the community have concerns about. Gilead's recent focus is more on Biktarvy (bictegravir/FTC/TAF).

Gilead are looking at long-acting options (injectables or maybe implants, but that is less likely initially), using a novel class of drug (a capsid inhibitor). They are looking for another drug to partner with this, and have purchased some broadly-neutralising antibodies (bNAbs) that appear to be promising.

Gilead have a TAF version of Truvada (FTC/TDF) for PrEP called Descovy (FTC/TAF). They presented data showing the efficacy and safety of this TAF version,

Gilead have a treatment for COVID-19 called remdesivir, which has been approved for use in the USA and in the UK. This appears to shorten the length of time a patient may need to stay in intensive care, but does not appear to have a beneficial effect on the mortality rate. They showed results from their studies on remdesivir, as well as data from the WHO study on remdesivir.

With hindsight, the UK-CAB asked too many specific questions. Gilead were rushed for time at the end, and raced through a lot of slides. In future, we may want to focus down on those studies that are of particular interest - or of particular concern.

1. Background

We have not had a meeting with Gilead for over 2 years. The UK-CAB was therefore keen to get a view of Gilead's trials using their current products, as well as learning about what was in their pipeline. We asked some rather specific questions as well as more general ones. We also asked Gilead to update us on the use of remdesivir for treating COVID-19.

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

2. Meeting

- **a)** Introduction to Gilead
- **b)** General HIV questions
- **c)** COVID-19
- **d)** Specific HIV questions

a) Introduction to Gilead

Sylvia Alfred spent 15 minutes telling us about Gilead, the company.

She said that Gilead is committed to providing access to people who need Gilead medication around the world. They have patient assistance programs and drug donations in the US. They work in nearly 140 resource-challenged countries.

Gilead support worldwide efforts to eliminate HCV by 2030. More than 2 million patients living with HCV have been treated with Gilead medicines.

15 million people living with HIV are estimated to be receiving a Gilead-based treatment.

Gilead is "a global philanthropic leader": $380M donated globally in 2019, with another $28M in the US.

There is more information about the company and its mission and core values on the Gilead website: www.gilead.com/purpose/mission-and-core-values

She was asked whether the pandemic crisis and funding for COVID-19 support would impact future support for HIV community work. She replied that Gilead HIV community support would continue.

b. General HIV Questions

Q1: What is your long-term strategy for HIV treatment? Companies are focusing on reducing the number of ARVs needed from 3 to 2 – what are your plans in this area?

Gilead is still "assessing the evidence" around 2DC vs TT - two drug combinations (2DCs) (such as ViiV's dolutegravir-based Dovato (dolutegravir/lamivudine) or Juluca (dolutegravir/rilpivirine)), or triple therapy (TT) (such as Gilead's Stribild (elvitegravir/cobocistat/emtricitabime/tenofovir DF) or Biktarvy (bictegravir/emtricitabine/tenofovir AF)).

"At this point, we (Gilead) believe TT outweighs the potential risks with 2DCs, whereas 2DCs have not demonstrated benefits over Gilead's TAF-based TT."

Although they didn't show it, Gilead had a poster at the BHIVA meeting, suggesting that there was less risk of discontinuation due to treatment failure with TT compared with 2DC (VACH2 study). But many other posters showed how 2DCs were very effective and safe, over long time periods

When asked about what the potential risks are, Gilead replied with concerns about low-level viraemia and long-term ongoing inflammation.

We also asked about weight gain. Gilead said that they weren't really going to talk about this, since we hadn't sent them a specific question about this. But they did make some observations:

- Comparing studies is difficult - they all have different populations and starting points. For example, someone treatment naïve and starting ART late will likely gain weight as a result of getting healthier.
- Different ethnicities may have different cultural views about weight and may not see weight gain as a problem.
- Everyone tends to gain a bit of weight as they age (about 0.8kg/year?).
- TDF and TAF have different results with weight gain. TDF shows a slight decrease in weight; TAF a slight increase.
- Weight gain in treatment naïve studies is higher than in switch studies.
- There does seem to be some evidence that integrate inhibitors lead to more weight gain than other classes of ARVs, though all show some weight gain.

For long-acting injectables (LAI), there is concern about the long half-life of the drug - the length of time the drug stays in your body. There may be problems when you stop taking LAIs if there is a low level of drug still in your system. We asked about implants, which are commonly used by some women for contraception. Newer types of implant can release drug intermittently into the blood, so perhaps avoiding the need for drugs with long half-lives.

Q2: You presented at the recent Glasgow conference on the capsid inhibitor (CI) lenacapavir (LEN), dosed six- monthly, (having a high barrier to drug resistance and no cross-resistance to other classes.) There was no reference to which other long-acting drugs would be used with lenacapavir – is there any news on this? Could you characterise the ideal drug?

Gilead are looking for a drug that would have synchronicity with the CI…in other words, also need dosing only every 6 months.

We know cabotegravir (CAB) from ViiV has been undergoing trials and seems effective for 2 months, but this would not be a good match, and anyway, Gilead said that they would prefer to develop their own drug rather than work with another company.

Any drug would also need the other characteristics - low volume, subcutaneous injection, high barrier to resistance…and maybe with the possibility for self-administration. Though not mentioned at this point, it came up later in the discussion about broadly-neutralising antibodies (bNAbs). Gilead has purchased two bNAbs from Rockefeller University that seem to have similar long activity to LEN, so this might be a possible partner, and an area that Gilead might be exploring.

Q3. What do you see as most promising in long-acting ARVs - injectables or implants, and why?

This was discussed a bit previously (see above). Gilead raised the concern about the different rates of metabolising some ARVs in different ethnicities; for example, we know that efavirenz (EFV) is slower to metabolise in black African women. This might lead to concerns with long-acting injectables or implants.

Q4. 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. Specifically, what is the current participation of women in clinical trials?

Gilead said that things were improving, but still not ideal. They highlighted a number of trials that were for specific populations that had perhaps been under-represented in early trials. Early trials tended to be predominantly with white gay men, so black populations and women were historically under-represented. BRAAVE is a trial in the US for black Americans using Biktarvy (bictegravir/FTC/TAF); and there are other studies or sub-studies on:

- older populations;
- people with renal disease;
- people with resistance to many other ARVs.

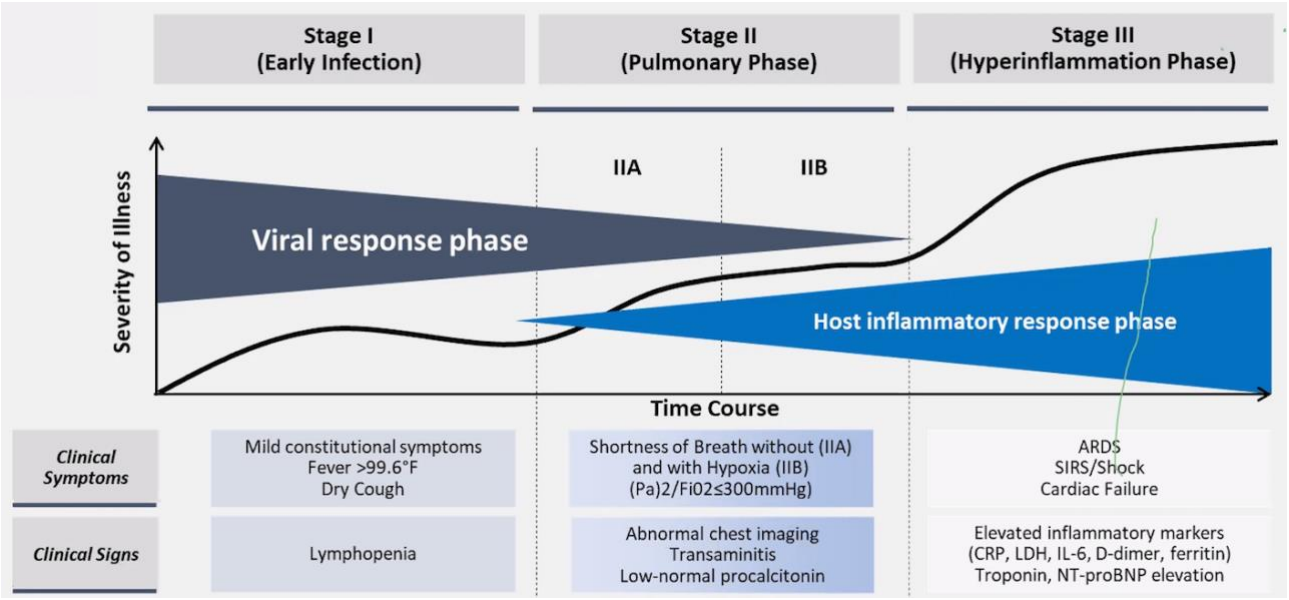
They also highlighted studies done in Africa that involved the community at all stages of the trial. They mentioned the North American Community Advisory Group (CAG) for community engagement (CE): a cohort of 16 representative leaders in HIV advocacy, research, policy and direct clinical service provision…which is not quite the same as the UK-CAB, but does have some community representation. There is also a women's PrEP study using LEN, and also FTC/TAF (Descovy - emtricitabine/tenofovir AF (FTC/TAF)).

c. COVID-19

William McCully presented this section on COVID-19. He started by highlighting that there have been several trials using remdesivir (RDV), but focussed on the SIMPLE trials (using Gilead product, though not run by Gilead). The results have been published in a reputable scientific journal (New

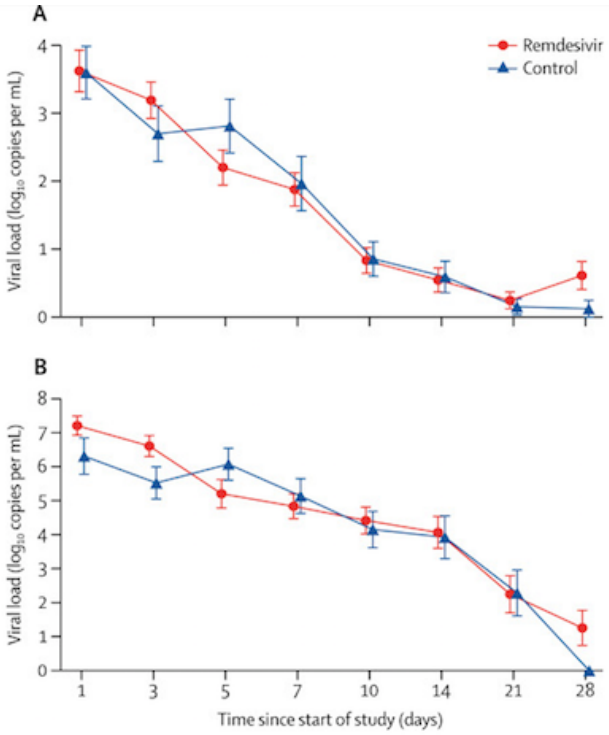
England Journal of Medicine). This study compared 5-day vs 10-day dosing vs standard of care (SoC) in people with moderate COVID-19 pneumonia but without reduced oxygen levels. The primary endpoint was based on a 7-point scale of clinical symptoms at day 11.

The results reported that 5-day treatment significantly improved outcomes at day 11 compared to the control arm, but results for the 10-day treatment however were not significantly different from the standard of care arm. But mortality rates were not much different between all the arms. So using remdesivir seems to shorten the time someone might be in intensive care, but may not reduce the chance of mortality. This would ease pressure on ICUs.



Covid-19 appears to have distinct phases, illustrated by this Gilead slide:

Remdesivir is an antiviral, so needs to be given early to be effective. A UK-CAB member asked about the results of a Chinese study, which showed that RDV had no impact in terms of lowering the viral load in patients:



(Wang Y et al. : Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multi-centre trial. Lancet 2020; 395:1569-78.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31022-9/fulltext

The graphs are Figure 3: Viral load by quantitative PCR on the upper respiratory tract specimens (A) and lower respiratory tract specimens (B))

Samples were carefully taken from nose and throat. Gilead could not explain this lack of effect.

The WHO SOLIDARITY trial was described. Launched in March 2020, the SOLIDARITY study randomised 11,266 participants hospitalised with COVID-19 to one of four groups:

(i) remdesivir (n=2750),
(ii) hydroxychloroquine (n=954),
(iii) lopinavir/r (n=1411) and
(iv) interferon-β1a, or to a control group receiving standard of care in each country but without any of the study drugs, even if available (n=4088).

The study was run at more than 400 hospital sites in 30 countries and required minimum reporting other than survival outcomes and a few baseline characteristics. This limits the data available for interpreting more complicated results.

None of the study drugs reduced the number of deaths compared to the control arm. The researchers report that "this absolutely excludes the suggestion that remdesivir can prevent a substantial fraction of all deaths (the results are) compatible with prevention of no deaths". Gilead challenges this, citing the simple trial design and differences in standards of care.

The issue is still controversial. There are a number of other trials still ongoing wrt covid, using HIV ARVs and bNABs, amongst other treatments. But there is no evidence to suggest that HIV ARVs have any beneficial impact in the treatment of covid.

d. Specific HIV questions

Q5. We note that elvitegravir requires boosting by cobicistat, and is typically used in combination with other drugs such as emtricitabine and tenofovir. We understand that you have been looking at the use of this combination, but switching from TDF to TAF, in a number of situations including:

- *In adolescents*
- *In people with mild renal impairment*
- *Comparing the TDF and TAF combinations in treatment naïve patients*
- *In HBV connected*
- *In older population (≥60years)*
- *In other switch studies.*

Could you give us a brief summary of the outcomes, and what your view on the use of this combination is, going forward? Are there concerns about the continuing use of boosters?

Gilead presented a lot of data, with graphs for each of these sections. But time was running out, so they rushed through these slides at a terrific pace. However, the slides (when approved by Gilead) will be available on the UK-CAB website. A summary of the results is given here.

The suite of studies involving the use of elvitegravir is one of the largest undertaken by Gilead, so there is a lot of data. But the message in all the studies is that the elvitegravir combination, typically Genvoya (elvitegravir 150 mg/cobicistat 150 mg/ emtricitabine 200 mg/tenofovir alafenamide 10 mg) is safe and effective in all of these situations.

But Gilead also said that their focus now was more on Biktarvy. Biktarvy is a fixed-dose combination of an integrase inhibitor, bictegravir, in combination with two other drugs: bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg (BIC/FTC/TAF).

There is concern about the use of boosters like cobicistat, not so much from the efficacy point of view, but more about concern for drug-drug interactions. Gilead presented data on switch studies from Genvoya to Biktarvy, which showed that Biktavy was effective, well-tolerated, with no virological failure and no treatment-emergent resistance, with similar changes in weight (slight gain).

Q6. Biktarvy and switch studies, presented at CROI (Black Americans and Older Adults) and Glasgow conference (switch studies from Boosted PI-Based regimens; aged 65 years and older; BICSTaR safety profile) – a brief update please.

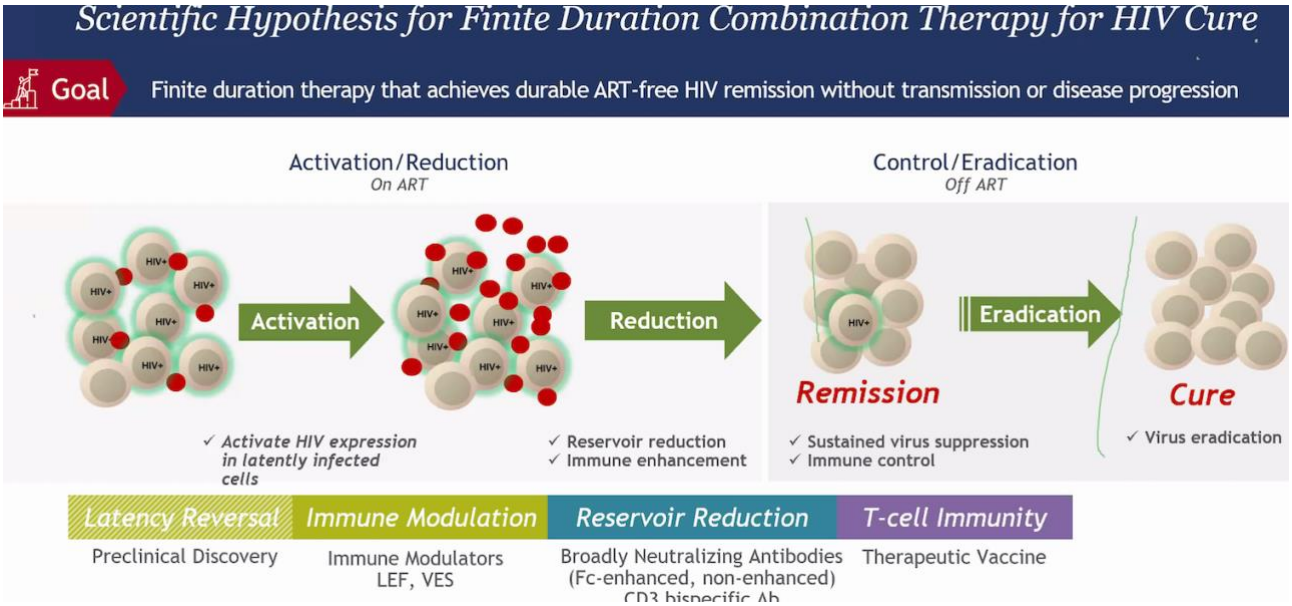
The BRAAVE study looked at switching HIV-suppressed Black adults from a triple therapy of 2 NRTIs and a third agent to Biktarvy.

Biktavy was effective, well-tolerated, with no virology failure and no treatment-emergent resistance. However, after a year, there was 3kg weight gain, compared with less than 1 kg in the other arm.

BICSTaR looked at real-world data (a cohort study) to evaluate effectiveness, safety and tolerability of Biktarvy in routine clinical practice, with 1400 patients in Germany, France, the Netherlands and Canada. It was highly efffective, regardless of age, gender and CD4 count, and was well-tolerated.

Q7. Please update us on your HIV cure and HIV vaccine research, including on bNAb combination (GS-5423, GS-2872)?

Gilead said that they were not involved with vaccine research. They described their approach to cure research in the attached Gilead slide, but did not have time to go into detail:



Gilead showed "proof of concept" data using bNAbs in primates, and described some phase 1 and planned phase 2 ATI (antiretroviral treatment interruption) studies using bNAbs and also LEF (lefitolimod), a TLR9 agonist (TITAN and AELIX-003).

Q8.1: Please update us on the recent results from the DISCOVER trial, using Descovy for PrEP. You recently reported results on:

- *Impact of age and co-morbidities on renal outcomes*
- *A novel statistical method of estimating HIV incidence*
- *Safety of FTC/TAF vs Descovy (FTC/TDF)*

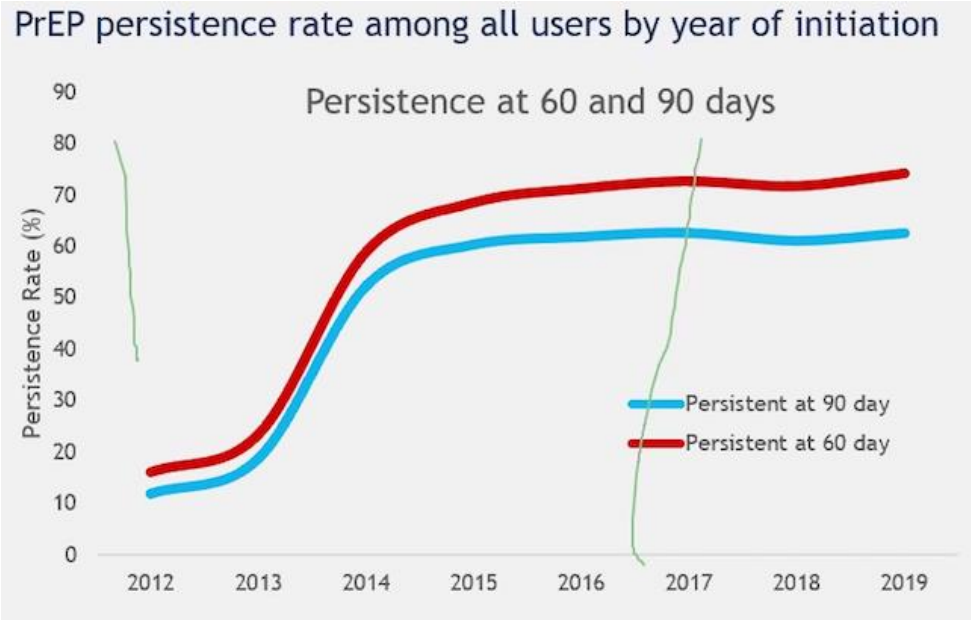
Gilead described the DISCOVERY trial, for MSM (men who have sex with men), with high sexual risk of HIV, switching from Truvada (FTC/TDF) to Descovy (FTC/TAF).

FTC/TAF was non-inferior to FTC/TDF, and associated with an improvement in or smaller decline in eGFR (estimated Glomerular Filtration Rate - a measure of how well the kidneys are performing). TAF showed an improvement in renal biomarkers, suggesting less damage from TAF (if any) to kidneys, compared with TDF.

There was also an improvement in bone mineral density in going from TDF to TAF. There was a slight weight gain (about 1kg) in switching to TAF, though.

Q8.2: You recently presented data on the persistence of Truvada for PrEP - real world data. Please update us on this.

PrEP persistence means the consistent use of PrEP during periods with the potential for exposure to HIV. Persistence is the opposite of drop-out rate, which is more usually reported on. Gilead presented data showing that persistence using Truvada (FTC/TDF) had increased over the past decade, but has been relatively stable for the past few years.



(Gilead slide)

There are many reasons why people may stop taking PrEP, which are be unrelated to the ARVs being taken. These can include changes in lifestyle or relationships, and stigma or peer pressure. But this study suggested that there were also some discontinuations due to problems with kidneys, or with bone fractures.

This is a prelude, to Gilead wanting users to switch from Truvada (FTC/TDF), to Descovy (FTC/TAF), though Gilead at this point did not say that… In any event, if there were concerns about the use of TDF for PrEP (for example, in people who are known to have kidney disfunction), then Descovy could be considered rather than Truvada.

UK-CAB Participants

	Name	Organisation	Destination
1	Alex Sparrowhawk	THT/UK-CAB SG	Manchester
2	Ben Cromarty	Yorkshire Mesmac	Northallerton
3	Damian Kelly	P.A.A / UK-CAB	Manchester
4	Grace Chigaru	Individual	Caterham
5	Husseina Hamza	Red Ribbon Living Well	London
6	James Dunworth	HIV I- Base	London
7	Jo Josh	BHIVA, UK-CAB Steering Group, Co-Chair Sophia Forum	Surrey
8	Jose Mejia	METRO Charity	London
9	Memory Sachikonye	UK-CAB	London
10	Mercy Nangwale	Individual	Luton
11	Meriel Rattue	Individual	Watford
12	Mesfin Ali	Embrace UK Community Support Centre	London
13	Shiellah Mushunje	Dhiverse	Cambridge
14	Simon Horvat-Marcovic	Positively UK, THT	London
15	Simon Collins	HIV I- Base	London