Thursday, 27 February 2020

(10.30 am)

SIR BRIAN LANGSTAFF: Can I before they are sworn, once again welcome a panel of distinguished experts, two of whom you have already met during this week, those of you who were here yesterday, welcome back. But welcome to the other four. I know that you are all busy practitioners and so we are especially pleased that you have made time in busy timetables, with other responsibilities, to be here to help us. Thank you.

May they be sworn.

PROFESSOR GARETH TUDOR-WILLIAMS (affirmed)

PROFESSOR GRAHAM COOKE (sworn)

SIAN EDWARDS (affirmed)

DR DAVID JOHNSTON (sworn)

DR IAN WILLIAMS (affirmed)

PROFESSOR JANE ANDERSON (affirmed)

SIR BRIAN LANGSTAFF: Ms Scott.

Examined by MS SCOTT

MS SCOTT: I am going to start by asking you to introduce yourselves and say a bit about the experience and expertise that you bring to the Inquiry, but can I start, first of all, with

you, Professor Tudor-Williams, with an apology that you have been demoted on your name tag up there to Dr, but to reassure you that your correct title has been put in the report. So can I start with you.

PROFESSOR TUDOR-WILLIAMS: Well, let me say I am a doctor, and I'm a paediatrician, and I first looked after a child that we diagnosed with HIV at Saint Mary's Hospital along the road in Paddington in 1988, and since that time I have been working with children and young people infected and affected by HIV. I spent five years in America specialising from 1989 to 1994, and since then I returned to join an extraordinarily accomplished group of colleagues running a family clinic for HIV infected children and young people, and now adolescents and people in their 30s who are still from our surviving cohort. Thank you.

MS SCOTT: Professor Cooke?

PROFESSOR COOKE: I am Graham Cooke. For those who weren't here yesterday, I have been working with patients living with HIV for over 25 years. I am based at the same institution as Professor Tudor-Williams and my focus really is

on co-infection. I lead the co-infection services in that hospital and the majority of my time now is spent on research, particularly around co-infection and the aspects of HIV, including HIV diagnosis and cure work.

MS SCOTT: Ms Edwards?

MS EDWARDS: Hello again. So my name is Sian Edwards. I started HIV work as a clinical nurse specialist, a bit of a misnomer at the time, which was in 1986 in Sydney. I came over and spent lots of the subsequent years in Zambia in Africa and in London and Australia doing education and clinical work teaching nurses and to care for patients with HIV and AIDS infection.

I also spent five years as a clinical nurse specialist in the haemophilia unit in London at St Thomas' Hospital and one of the reasons that I think I have been brought in by the Inquiry is because I undertook two research projects with people with haemophilia and HIV, which many of you know of, looking at people's life histories and the experiences that they had been through and then a second project with people who were the relatives and the family

members of those who had died of AIDS who also had haemophilia. I'm currently based in Melbourne in Australia.

MS SCOTT: Dr Johnston.

DR JOHNSTON: Good morning, my name is David Johnston. I'm a general practitioner and I have been a general practitioner for 25 years. During that time I have been involved in a number of community initiatives and have also been involved in researching rural and isolated practice, so I believe I bring to the Inquiry the perspective of a generalist, a non-specialist, if I can use that term, so thank you.

MS SCOTT: Dr Williams?

DR WILLIAMS: My name is Ian Williams and I have been involved in the care of patients with HIV since 1987. I have been -- I am a consultant in *(unclear)* medicine and a clinical academic and have been directly involved in out-patient care and in-patient care first at the Middlesex Hospital, then at University College London Hospitals and I continue to do out-patient work. I have been chair of the British HIV Association and my clinical academic role has largely been

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in treatment trials of anti-retroviral therapy.

MS SCOTT: Professor Anderson?

PROFESSOR ANDERSON: Thank you, good morning. I first trained at Saint Mary's Hospital. I'm a doctor. I specialise in HIV infection and I trained at Saint Mary's Hospital and first met somebody living with HIV in 1984 when I qualified, and I continued doing my junior doctors years working in infectious diseases and was appointed a consultant in HIV medicine at St Bartholomew's Hospital in 1990. I helped set up the first HIV unit at Barts and also worked at Homerton during that time.

In 2004 I moved across to Homerton Hospital where I still practice in Hackney. I have been particularly interested in the care of women and families and, because of the population who use our clinics in East London, I've been interested in black and ethnic minority communities and in migration. Other roles: I have also been chair of the British HIV association, like Ian, and I currently chair a national campaign on policy charity, the National AIDS Trust.

MS SCOTT: Thank you. You have been provided with

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two letters of instruction from the Inquiry and a summary of some of the evidence given to the Inquiry. You have provided a report to the Inquiry and you are due to answer some of the questions that were raised in the supplementary letter of instruction in a supplemental report; is that right?

PROFESSOR ANDERSON: That's right.

MS SCOTT: The report that you have provided is that a report that all of you have read and all of you agree with the contents of?

All agree.

MS SCOTT: There are no areas of disagreement between you.

All agree.

MS SCOTT: Can I start then by asking questions about what HIV actually is, and I'm going to ask them generally so anyone that wants to answer them do feel free to answer.

PROFESSOR ANDERSON: Where shall we start? HIV is a virus which is an infectious agent and it belongs to a particular family, the retroviruses, and it particularly affects white T cells, the T lymphocytes, and its effects mean that when it infects somebody and gets into the

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cells, the immune system becomes damaged and disordered. Essentially, it's an infectious agent that is particularly affecting the immune system of human beings. It comes in two main sorts, HIV-1 and HIV-2, which are quite significantly different and the treatment of the two is different. HIV-1 has got a variety of subtypes within it but we have some major subtypes which are the most common ones, and it appears that the natural history, what happens to somebody with the different subtypes of HIV-1, is pretty similar across all of them.

MS SCOTT: What are the differences in terms of what are the clinically significant differences between HIV-1 and 2?

DR WILLIAMS: HIV-1 is responsible for the main pandemic across the globe. HIV-2 is largely limited to West Africa but can be imported into other parts of the world. HIV-2 doesn't have the same natural history. It's a much more -- it doesn't have the same impact in terms of clinical consequence as HIV-1.

PROFESSOR ANDERSON: I think the other thing I would add to that is the structure and the way the virus is, the structure of the virus, means that

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some of the drugs that work for HIV-1 don't work properly for HIV-2 because the virus is of a different enough structure for the molecules not to sit in the right areas and work as well.

MS SCOTT: Is that the same the other way round? Some of the drugs that worked for HIV-2 don't work for HIV-1?

PROFESSOR ANDERSON: It hasn't worked like that because, as Ian I think has alluded to, there are far fewer people living with HIV-2 and so at the moment there are no specific drugs being designed for HIV-2. It's using the HIV-1 drugs in a way that is most appropriate for that virus.

MS SCOTT: Again, in terms of the different subtypes of HIV-1, are they clinically significantly different?

DR WILLIAMS: No, not really.

MS SCOTT: How does a person become infected with HIV? What are the infection routes?

PROFESSOR ANDERSON: Where shall we start? Worldwide, the most common route of infection is through sexual transmission and that can be from vaginal sex, from anal sex, from oral sex. So sexual transmission and sexual fluids are the

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most common route of transmission.

It's also transmissible by blood, blood products and it can also be vertically transmitted from a mother to an unborn child, and it's also transmissible by breast milk. The other modes of transmission, so, for example, people who use intravenous drugs, that will be a microinfusion of blood, so that's blood to blood transmission usually. So sex, blood, vertical, and breast milk. Have I missed anything out?

DR WILLIAMS: No.

MS SCOTT: What is the extent of viral exposure a person requires to become infected? You mentioned a very small amount. Could one particle of HIV infect somebody?

PROFESSOR ANDERSON: I don't know whether, Graham -- we had been putting some of that --

PROFESSOR COOKE: I think we will summarise some of this in the supplemental responses but, yes, that is broadly the case and, therefore, the risk of being infected depends very much on a number of factors, including the quantity of virus that an individual is exposed to and the proportion of that batch or product that may

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have been administered. The risk of infection is then balanced by also the individual's susceptibility to be infected. So not all individuals are similar in their ability to be infected and sometimes a similar exposure may or may not result in infection itself.

DR WILLIAMS: Just giving a sense of that, if you look at sexual transmission, then maybe 1 in 300 times when you might have a risk of sexual transmission, so about 0.3 per cent, while if you have a transfusion of infected blood product then that's clearly -- you know, the likelihood of infection is uniform. If you have a sexual exposure then not everyone who has sexual exposure will get infected.

MS SCOTT: So could it also be the case that if you had a number of people exposed to a batch of infected blood or blood products, not all of them would become infected?

DR WILLIAMS: Correct.

PROFESSOR COOKE: Yes, I think that is possible. I think without going into too much of the small print, then, for example, there are a small proportion of individuals who carry particular genetic variation who may actually be refractory

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to infection. That's quite unusual. It varies across populations but in a Caucasian population maybe 1 per cent of individuals may carry that mutation. If they have two copies, it might be very hard to be infected and there is evidence that such individuals tend to be overrepresented in groups where there's been exposure without infection. But I don't want to suggest that's the most common reason. It's a relatively unusual issue.

PROFESSOR TUDOR-WILLIAMS: I'd just like to add from the perspective of a paediatrician, the data suggests that drinking 1 litre of breast milk from an HIV infected person who is not on anti-retroviral treatment would carry the same risk of transmission as one unprotected vaginal intercourse. So about 1 in 300 risk from 1 litre of breast milk, just to give you an idea that other body fluids are implicated.

MS SCOTT: Would repeated exposure to infected products increase the risk of a person being infected, so somebody that hadn't been infected on exposure 1, would that mean they wouldn't become infected at all on exposure -- up to exposure 10, or would that increase the risk?

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PROFESSOR COOKE: So, in general, yes, but I think with the caveats that actually there may be a small minority of individuals who are naturally resistant and actually won't get an increased risk of infection with more exposure, but in general that increased risk of exposure is likely to increase the risk cumulatively over time in broad terms, and I think in our supplemental report we'll go into a bit more detail about that.

MS SCOTT: Does anyone else want to add anything on that?

DR EDWARDS: Just the other added exposure, of course is the vertical transmission. So although somebody may be HIV positive, it does not mean that their baby will naturally be infected, and obviously treatment changes that a lot, but in the early days prior to treatment we were talking 15 per cent.

PROFESSOR TUDOR-WILLIAMS: The data would be -- if a person infected with HIV doesn't know their diagnosis has a vaginal delivery and breastfeeds that child, about one third of those babies would be infected. But it very much depends on the maternal viral load, and it could be as much

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two thirds if the mother has a very high viral load.

MS SCOTT: Is it possible to have HIV 1 and HIV 2 in one batch of infected blood product?

PROFESSOR ANDERSON: It's certainly not impossible. It would depend -- certainly there are people who are living with both viruses, and so it would be, I think, very unusual, but I wouldn't like to put a figure on it, but not impossible.

MS SCOTT: So if there are people living with both viruses, are there people living with different types of -- subtypes of the virus as well?

PROFESSOR ANDERSON: That's more complicated.

DR WILLIAMS: I think the -- subtypes are difficult because the virus evolves quite quickly in the body. It replicates very rapidly. It doesn't proofread itself, so it makes -- errors are introduced and, therefore, you get a very broad sort of quasi-species within the -- within the person who is infected, and so you may get a subtype, but they could be known as recombinants, which are basically where viruses have come together. But it's largely -- you can generally determine whether someone is a subtype B or subtype A generally from -- from their DNA

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analysis.

PROFESSOR TUDOR-WILLIAMS: I think it is worth saying that in the early days, I certainly remember back in the '90s, there was reports coming out of various corners of the world, including India, where they were claiming that there were all sorts of people infected with HIV-1 and 2, which was a complete misconception based on the fact that the test was picking up antibodies to either HIV-1 or HIV-2. It was reported as positive for HIV-1/2, and people were being -- there were physicians who believed that that meant you got both viruses, and that simply was not true. In fact I think in the UK I simply don't remember a single child that we have looked after over 25 years who had both viruses.

PROFESSOR ANDERSON: Certainly people can -- I think Gareth is absolutely right, the testing and the technology and the laboratory differentiation of the different sorts of HIV-1 or 2 has become much more sophisticated, and those early tests may -- often came back as a report which didn't necessarily differentiate. So I think that's a very fair comment. But in today's world you

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can differentiate them and we know that for certain parts of the world there are people who are living, definitely, with both 1 and 2.

PROFESSOR COOKE: Just to add a couple of points. I think in our routine practice it's very unusual to see patients with both HIV-1 and HIV-2, but I think -- and -- so from a single donor, for example, that would be an unusual thing. But where you've got products pooled, as we discussed yesterday a little bit around hepatitis C genotypes, then it theoretically could be possible for more than one type of HIV to be present.

I suppose the other thing that might be helpful to talk about is super-infections. So it is possible, once you have an infection with HIV, to have a super-infection if you have a further exposure, and we see this particularly with sexual transmission, even now, and then in that situation you may have more than one type of the HIV-1 in circulation. It doesn't necessarily have big implications, we may come on to that, but it is definitely possible.

MS SCOTT: So super-infection relates to infection with a different type of HIV?

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PROFESSOR COOKE: Where you can distinguish that virus from the one the patient originally had.

MS SCOTT: Presumably -- well, does repeated exposure to the same batch of infected product then, would that increase your viral load? Does that change the nature of your infection?

PROFESSOR COOKE: I think we've tried to find evidence of this. I don't know if -- so we found relatively little evidence to suggest that the viral load will change but I think if people are aware of other evidence that would be helpful.

DR WILLIAMS: I don't think the viral load would change. That very much depends on how the immune system of the individual who is infected responds to HIV and how well that protective immunity develops, and so the exposure to HIV and the inoculum with HIV in it -- well, you know, so the route of infection does not determine the natural history of HIV or the individual's response, right. It will determine the risk of acquiring HIV in terms of the size of the inoculum, which would be much greater with the blood product than it would be for sexual exposure. So the risks would be --

definitely be different but in terms of how the immune system then responds to that inoculum will be dependent on other factors, viral and host factors, which are -- we can go into.

MS SCOTT: Perhaps we should go on now then to the stages of infection of untreated HIV as you deal with it in your report. You identify three stages: early infection, or acute or primary infection; chronic infection; and then advanced infection.

So if you can just start with early infection. How is this characterised? What is happening when somebody is first infected, in terms of the virus and in terms of their immune response?

DR WILLIAMS: When someone first acquires HIV, the immune system will respond like it will respond to any infection. It will recognise that infection and it will be activated, and it will try to produce an immune response to that, and it -- generally that immune response can be detected after about two to four weeks following infection. So those anti -- those responses can be divided into largely a response by producing antibodies, which tends to protect or fight

infection within cell-free virus, or produces responses that are cell-based, and that's -- produces -- fights against infection within cells.

That -- so that's the reason we use an antibody test to determine whether someone is infected, because that tends to become positive after two to four weeks and then evolves.

After that two to four weeks, people -- the viral load in someone, the amount of virus, it replicates. It starts at the area where it was first inoculum then spreads throughout the body, and it will cause -- replicate in high levels and the viral load in someone with primary infection is likely to be very high, in the figure of millions, as opposed to someone with a -- who's got a chronic infection, where it will be in the thousands or tens of thousands.

Then the immune system kicks in and tries to control the virus, as it would do with any infection, but because of the way -- how the virus affects the immune system, the immune system fails to do an adequate job, it fails to clear the virus. But the quality and the

strength of how someone responds to the virus is dependent on genetic factors, and so someone can clear the virus down to very low levels and other people they don't develop a very good immune response and they have a very high viral load after three or four months. But during that first two to four weeks someone can be unwell, with symptoms of primary infection, and those symptoms are things like fever, headache -- like flu-like symptoms, often unrecognised or sometimes quite severe.

MS SCOTT: So in your report at page 21 you say this about the symptoms at that initial stage:

"Symptoms most frequently described are a raised temperature, a sore throat, mouth ulceration, enlarged lymph nodes, aching muscles and joints and tiredness. A short-lived pale pink rash is sometimes seen. Nausea diarrhoea and weight loss can occur. Neurological symptoms are common and may include headache and aversion to light, photophobia."

Are those fairly common side effects -- I mean, symptoms at this stage?

DR WILLIAMS: Yes, they are. Because they are very much like flu-like symptoms, which people might,

you know, get for -- with flu or similar viruses, they often go unrecognised. So, for example, in clinical -- in clinics, people presenting with primary infection is uncommon. People often get diagnosed much later. So we would -- you know, in terms of the -- it's far more common to get diagnosed with established infection than to present with primary infection because those symptoms which we have described are very similar to many other flu-like symptoms or glandular fever or something like that which people may not seek medical help with and, therefore, the diagnosis goes undiagnosed.

MS SCOTT: And some people will report no symptoms; is that right?

DR WILLIAMS: Yes.

PROFESSOR ANDERSON: Although, interestingly, when -- quite often if you -- when you do meet somebody who is newly diagnosed, asking if they have ever had a set of symptoms like this, more people than you might expect will say, "Actually, yes, it does jog a memory". So even if they haven't presented to clinical care, on closer questioning with a diagnosis people may recall having had something.

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MS SCOTT: You go on in the report to say this:

"In rare cases there may be signs of meningitis or of direct brain infection. In most people the illnesses last up to three weeks and resolve on their own and recovery is usually complete."

So in those rare cases where there are more significant symptoms, do those symptoms also resolve on their own or do those continue?

DR WILLIAMS: No, I mean severe primary seroconversion illness or primary infection can last several weeks and it can result in hospital admission, particularly those with meningitis, so it can be a differential diagnosis of somebody presenting with meningitis. It's part of how the immune system is responding to the infection. Some people, it can affect the immune system so severely that they develop an AIDS defining illness primary infection, but that is really quite uncommon in terms of presentation to hospital. But, yes, it can be quite severe and it can last several weeks in terms of symptoms but it does resolve.

PROFESSOR TUDOR-WILLIAMS: Can I just add the only difference in children is that if you acquire

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HIV in the perinatal period then unfortunately this is a neurotropic virus and if it hits your brain as it is developing that often had life-long consequences. That wasn't so true for children meeting the virus for the first time during childhood outside the perinatal period but it's a very well-recognised consequence in the natural history of HIV in perinatal transmission from mothers to children.

MS SCOTT: We heard yesterday about a window period when we were discussing hepatitis. Is that relevant to HIV and, if so, what is it and why is it relevant?

DR WILLIAMS: It's relevant as I said before you develop symptoms of primary infection when the viral load in someone is quite high but the immune system has yet to develop sufficient antibodies to be detected by the assays that we use to diagnose HIV. So there used to be a period where from the last possible exposure to HIV to then having a test used to be a window period of three months in terms of if someone had had a potential exposure to HIV in that period of time we would say we would want to wait until at least three months after that

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exposure to get a test.

The more modern assays that are now employed the fourth and fifth generation assays, that is not so much the case. We can now identify someone with primary HIV infection two to four weeks after exposure because the more sensitive assays that we use do detect virus.

PROFESSOR COOKE: Just to follow up on that, and I think Dr Jefferey has summarised a lot of diagnosis development, but in HIV we have seen very good progress in terms of tests as Dr Williams is saying which detect both the immune response and the virus at the same time which are now routinely used and allow that early detection and narrowing the window, whereas that contrasts slightly with the development with hepatitis that was slightly behind.

MS SCOTT: You use the term in your report seroconversion. Can you explain what that means.

DR WILLIAMS: That's just from going to antibody negative to antibody positive, ie the detection of antibodies that are specifically aimed against HIV being detected by the diagnostic

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assays that we use.

MS SCOTT: So the acute phase you have described as lasting a number of months. What is it that marks the end of the acute phase and moving into the chronic phase?

DR WILLIAMS: I suppose after the seroconversion illness what happens is there's a balance that is struck between the virus trying to replicate and the immune system trying to defend and develop an immune response and so, as I said, as Jane has also alluded to, the virus attacks the cells in the body that are specifically important for co-ordinating the immune response to any infection, which are the T helper cells and these are very key in the co-ordination of the immune response, particularly adaptive and cellular immune responses, so what happens is the immune system is activated and it remains activated and it tries to constantly generate immune responses to HIV. In some people it can be very successful. In other people it's not so successful.

Those where it's more successful, then the virus is better controlled and the viral load in someone is lower. Where it's less successful

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the viral load is much higher and, to a certain extent, what happens during acute infection determines the natural history of HIV in an individual, so how your immune response responds to HIV during primary infection, during that acute phase, will determine your natural history because it determines how well your immune system is coping with HIV.

PROFESSOR ANDERSON: The time-line there, in general that bit of the process takes about six months to get to a steady state and so the arbitrary cut-off is that early infection is the first six months while these processes are going on and the viral load stabilises out to the viral set point and that sort of marks the end of early infection, if you like.

DR EDWARDS: It is worth noting as well with regard to this issue is that people are very highly infectious during that initial stage, so you have got highly replicating virus and so infectivity even though people may go through a test that is antibody negative the infectivity is particularly high.

MS SCOTT: So moving on then to the sixth month arbitrary six month point where we're at the

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chronic stage, the viral set point you've mentioned can differ between people. What are the factors then that contribute to that difference? In your report you said there are pathogen-related reasons and host-related reasons.

DR WILLIAMS: I suppose in terms of age it's by far the most important sort of host-related reasons because as you get older your immune system doesn't work as well as when you are younger and, therefore, you are likely to have a much better immune response when you are younger than when you are older, so age is definitely a factor in terms of that.

As Graham has alluded to, there are certain people who have genetically more resistance to HIV in terms of they don't express the certain receptors on their CD4 cells that make it much more difficult for HIV and there are other genetic factors that determine a person's immune responses to HIV in terms of how well -- like any infection, so if you take other infections, people can respond differently, their immune systems can respond. We don't all respond the same. Genetically we

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differ.

MS SCOTT: In your report you mention people with higher numbers of CD8 lymphocytes circulating and people who express HLAB57 markers having lower viral set points. Are those genetic factors?

DR WILLIAMS: Yes.

MS SCOTT: You have also in your report drawn attention to the presence of other infections having an impact on the host-related contribution to viral set point. Can you tell us a bit about that.

DR WILLIAMS: I think in terms of other co-infections, things like hepatitis B or hepatitis C don't have an impact in terms of how -- you know, in terms of how the immune system responds to HIV. It has an impact the other way round. Generally there aren't any other co-infections that will impact on the set point or on the natural history. There was data from a cohort looking at the cytomegalovirus in terms of whether that has an impact but that is not universally accepted. Generally, it's the quality and the strength of the immune response, which are genetically determined or age

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determined, that will determine the immune response to HIV. The subtypes makes no difference or the route of infection does not make any difference.

PROFESSOR ANDERSON: I would just add that some other infections will also be challenging the immune system at the same time, and so you may be seeing the effect of two separate processes, and so that may in itself be accounting for -- it may be more rapid CD4 decline but it is not necessarily working through the viral load mechanism.

PROFESSOR COOKE: Yes, a similar point. So I think you can see in the setting of another acute illness that someone's HIV viral load may rise transiently and usually come back again. But as we have heard, these sort of commonly recognised chronic co-infections tend not to have a big impact on that viral load.

MS SCOTT: Turning then to pathogen-related reasons I think you said the subtype doesn't have an impact but the type of HIV, 1 or 2, does that impact on --

DR WILLIAMS: Yes. I mean, everything we've written to should really be related -- this should have

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-- the title should be "HIV-1", not "HIV-1 and 2". Because 2 is really a very different disease, we see -- you know, it's something that only, you know, in the UK there's only 200 or 300 people who are infected with HIV-2 and it's largely only seen in West Africa or people who come from West Africa, so when we talk about HIV we are largely talking about HIV -- we are talking about HIV-1.

MS SCOTT: The other factor you mention in your report is the type of cellular receptor that the virus uses to enter the cells. It may be important as a factor in the progression of HIV. Can you tell us how that occurs?

DR WILLIAMS: HIV needs, as the report says, the reason why it is able to infect T helper cells, which are the specific type of white cells that are important for the immune response, is that those cells carry a molecule called CD4. It's the CD4 which the virus is able to attach to. But in order to gain entry into the cell it needs another co-receptor, which are determined chemokine receptors, and just for -- technically there are ones called CCR4, another one CCR5, and the virus can use one of those co-receptors.

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Generally a virus that is transmitted uses CCR5-bearing -- is tropic to CCR5 but later on in the natural history of HIV can use CCR4, it switches. It's usually CCR5. There are people who do not express CCR5 and they have a genetic deletion which means they do not express CCR5 and, therefore, they are people who are -- who are less likely to become infected with HIV but also people who are -- their natural history is much longer. They are, really, as Graham said, this is a small proportion in the UK.

MS SCOTT: So over this chronic stage then, what's happening to the virus and to the immune system?

DR WILLIAMS: If I could -- usually when the immune system responds to an infection it is activated and once the infection is gone the immune system goes back into resting state. But in HIV that doesn't occur because the immune system is constantly responding to ongoing viral replication and to other factors. So the immune system is in a state of hyperactivation and inflammation.

If I can give you a sense of -- if you were going to the gym and you were running on a treadmill you could walk quite comfortably for

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a long way but if you are having to run at a very high level you get exhausted much more quickly. That's what happens with the immune system. It basically is in a state of immune activation at a high level because there's this constant level of replication of the virus. So the patient remains clinically well but there's ongoing viral replication. So you are in a state of high inflammation and high immune activation.

MS SCOTT: Can I, Henry, ask you to pull up on the report page 6, table 1, please. Can someone tell us what this table is, what we're actually looking at here?

PROFESSOR ANDERSON: So this is one of the classification systems used internationally for HIV infection. This is one from CDC, the Centers for Disease Control in America, and is probably the most commonly used classification to try and describe where along the spectrum the infection has got to, going through some of the stages we have already discussed.

There are a number of classifications. The WHO have got one but this is the one that is the most commonly used when we're referring to

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where in the stage of infection people are.

So we have been talking so far about acute infection, early infection. Here we're talking about category A, which is the first column. Then we're talking about this latent period, if you like, chronic infection, where we talk about B. Then we get to a point which is classification C, which is where the HIV infection has now caused enough damage for somebody to get sick with a variety of particular clinical conditions which allows a diagnosis of AIDS to be made.

Now, in addition to that, there is the ability to put in the numbers of CD4 cells to modify that classification about whether somebody's got a very robust immune system, which is with the CD4 count above 500, or whether they are already in a place where the CD4 count is very low, i.e. below 200.

So this is really I suppose the international shorthand that is used in the world of HIV classification. It's probably, I would say, it's used much more as perhaps a public health and epidemiological tool as a way of charting what's happening, allowing you

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to compare populations. It's also important for an individual patient, to give them a sense of where on the spectrum they sit. So this is the recognised international classification.

MS SCOTT: In this chronic phase, this middle phase before AIDS is diagnosed, as I understand your report somebody could be showing no symptoms or somebody could be showing one or a number of the symptoms that are listed there in clinical category B.

PROFESSOR ANDERSON: Absolutely, yes.

MS SCOTT: Presumably people could move from no symptoms to symptoms back to no symptoms.

PROFESSOR ANDERSON: Yes, although on the whole if somebody has moved into early symptomatic infection often there's something grumbling around. It's --

DR WILLIAMS: Can I say, once they have gone into category B, that's an indication that their immune system has been damaged quite significantly so they can't move back to being asymptomatic.

PROFESSOR COOKE: It is worth just mentioning briefly again about the viral load in the CD4 account, so we talked a bit about T helper cells

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and when we talk about CD4 counts, we're talking about a blood test which gives an estimate of the numbers of concentration of those CD4 cells.

So the patient may be well and not have symptoms but their CD4 count may be declining and that is something that can be monitored. That tends to be the most useful test we can use to monitor that phase. The viral load is often measured. These days, patients would usually be on therapy but the viral load can give you some sense of progression risk but it doesn't tend to be what we use to monitor where things are going. CD4 count is the thing that's used mostly.

PROFESSOR ANDERSON: I think that's also important in the States and in some other countries of the world just having a CD4 count below 200 allows a definition of AIDS to be made. In the UK, you are required to have one of these clinical indicator diseases as well. So that's a difference between the American classification and ours, although in actual fact I think in practical terms it probably makes little difference because, as Graham is saying, by that stage your immune system is weak and you are

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susceptible to major infections.

MS SCOTT: When you talk about the clinical AIDS-defining diseases, what you mean is one of those in category C?

PROFESSOR ANDERSON: Exactly.

DR EDWARDS: It might be worth noting that although the classification doesn't change, you stay in that category. Of course, on a practical level you may well have medication and treatment that makes you feel better, your symptoms are less, but the classification remains the same.

PROFESSOR ANDERSON: Exactly.

DR EDWARDS: So you as a person may be treated and do not feel as sick as you were before but your immune system is still very compromised.

PROFESSOR ANDERSON: This, of course, presupposes this is without anti-retroviral therapy. This is the progression as untreated infection.

PROFESSOR TUDOR-WILLIAMS: Forgive me, we didn't put it into the report but there are different classification systems for children who, by and large, have rather more rapid disease progression than adults. The CDC came out with their classification system in 1994 and WHO revised that in about 2007 with a very

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comprehensive view of paediatric HIV that is different to this but it does fall into similar kinds of categories of ABC.

MS SCOTT: Again, the sort of acute, chronic and then AIDS.

PROFESSOR TUDOR-WILLIAMS: Yes, and recognising that actually in children it was even less common for the immune system to mount an effective response that produced symptomatic disease and indeed a less effective immune system that brought the viral load down, so that in perinatal infected children we were still seeing viral loads above 100,000 very commonly two years after -- you know, aged two.

Again, as you go through childhood beyond the age of 5 the CD4 counts broadly fall in line with adult CD4 counts. Below 5 children have very much higher lymphocyte counts and CD4 populations, so we had a whole different series of thresholds for recognising severe immune suppression in children.

We haven't put that all into the report. I am very happy to provide it in a supplemental report, if that's felt to be relevant.

MS SCOTT: So for children it takes them a lot

longer because their immune systems are immature?

PROFESSOR TUDOR-WILLIAMS: No, I wish that was true. No, quite the opposite, because you have got so many target cells, HIV replicates very, very efficiently in young children and, no, the fact that you've got a higher CD4 count just means that we had to adjust the threshold. I remember very clearly being told by my adult colleagues when we were diagnosing AIDS-defining conditions like pneumocystis pneumonia, in children with CD4 counts of 1,200 my colleagues would say, "Oh, don't be stupid. You paediatricians don't know what you're talking about". Actually, it turned out that the average six month old ought to have a CD4 count of about 3,000, and so 1,200 was already severely immunocompromised -- with all due respect.

MS SCOTT: Turning then back to the clinical category B, can we -- because the Inquiry has received and heard a lot of evidence about the different experiences that people had in the early days of HIV infection.

Can I ask you to go -- to explain what these clinical conditions are and how they would

be experienced by patients and what the treatment for them would be and, again, what the symptoms and side effects of those treatments would be.

PROFESSOR ANDERSON: You are talking here about the things that don't reach a classification of AIDS.

MS SCOTT: I am talking here about the clinical category B matters that are set out in this table 1.

PROFESSOR ANDERSON: So there's a variety here of conditions that are coming into play because the immune system is weakening, and it will depend, again, on each individual person which of these conditions comes to the forefront and which ones they experience. There are some particularly common things. Shingles (herpes zoster) is quite a common thing for people to experience early on because most people have at some point in their lives had a chicken pox infection, so it is a common virus that is in most people and actually it's quite pathogenic, so you don't have to be that immunosuppressed for it to reoccur. So it is one of the things that can come quite early on in category B, if you like,

because it is quite a powerful pathogen, it's common and you don't have to be that immunosuppressed to find it.

We noticed things like -- I have put here -- we have here idiopathic thrombocytopenic purpura. That is when your platelets in your blood are low and that's probably an autoimmune problem that's going on in the background so people might notice easy bruising or on a routine blood test, oh, the platelet count is looking low. The patient may actually not necessarily notice that but it may come up as a signal, if you like, there's something going on.

The sense of constitutional symptoms, people talking about just really not feeling great in quite a non-specific way and in those -- certainly in the days before anti-retroviral therapy it was not uncommon for people to talk about sweats, particularly night sweats, fevers and feeling just generally out of sorts and not well in quite a non-specific way.

Infections of the skin are quite common, flaky skin, seborrheic dermatitis on the face, quite common and infections of the mouth like

thrush and viruses that can affect the tongue causing oral hairy leukoplakia, which is an Epstein Barr virus. They are all quite non-specific in that setting but they are indicators of an immune suppression going on in the background.

Many of these now, and we come to this a bit later in the report, could be, if you like, indications as sign posts, signalling conditions, people who maybe go to their doctor with some of these conditions should be ringing alarm bells that there's something else in the background. But these are often not particularly specific to HIV but they are there as a marker that the body is not strong and something is going on in the background.

MS SCOTT: In the 1980s were treatments available for most of these conditions?

PROFESSOR ANDERSON: In the 1980s, it would depend. It was variable.

MS SCOTT: 1990s?

PROFESSOR COOKE: Some of them, but limited I think. Acyclovir would have been available, which would be a standard treatment for shingles (herpes zoster) and some of these would have responded

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to standard antibiotics like penicillin. The more common things -- and thrush and I think, in fact, there would have been some therapies, but when we come on to talk about the conditions of more advanced disease, those therapies were ones that needed to be develop specifically for HIV infected patients.

So of this list I would say actually probably most of them had some treatment available.

DR WILLIAMS: I think things like constitutional symptoms, which are really disabling, things like feeling very tired, diarrhoea, weight loss, night sweats, there weren't specific treatments for that because they were the direct effect of HIV damaging the immune system. Things like peripheral neuropathy, which is numbness in the feet, again, they were direct effect of HIV so it is only when anti-retroviral therapy came along that that made a direct effect on those.

Where you had a co-infection say with herpes zoster or with oral candida then that co-infection can be treated, but the constitutional symptoms were very difficult.

PROFESSOR TUDOR-WILLIAMS: It is worth pointing out

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there's a second page to the document that is on the screen at the moment.

MS SCOTT: Yes. Can we go down to the next page.

PROFESSOR ANDERSON: Candida.

MS SCOTT: Yes, so there are more conditions there on that second page. Can somebody speak to those.

PROFESSOR ANDERSON: So we talked briefly about thrush in the mouth and again people can get thrush in the mouth for a variety of reasons --

PROFESSOR TUDOR-WILLIAMS: Fluconazole was available.

PROFESSOR ANDERSON: We would have used nystatin mouthwashes, anvitosin mouthwash, anvitosin lozenges, do you remember those? Actually, sometimes Canesten pessaries we would use for people to suck and it would often give people a very sore mouth, be very uncomfortable, white tongue, white around the cheeks, lining of the cheeks.

The same for vaginal candida, again more difficult to treat than you would expect it to be, recurring, not shifting and, yes, there were certainly treatments available for vaginal candidiasis but not as effective as they are

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now, that's for sure.

Cervical dysplasia was added later on as it became -- more women became affected or were living with HIV. It became clear that more of them had got cervical abnormalities on smear tests and again they would have had standard treatment for cervical dysplasia at the time. Now with anti-retroviral therapy often those cervical changes go once a woman starts anti-retroviral therapy. Peripheral neuropathy I think as Ian alluded to, often really hard to treat and pain we would have used a variety of sometimes Amitryptolene in those days. There were not great specific treatments for people at that point.

MS SCOTT: Ms Edwards, did you want to out anything about nursing people at this stage of their HIV?

DR EDWARDS: I think the expression earlier about these constitutional symptoms were so very difficult and so debilitating in many ways. You know, oral candida, for example, is probably the classic because I know it looks awful. It's awful to treat. It stops you eating. It looks horrible. It's a very psychologically difficult thing to deal with and, of course, although

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other people get these infections, people with HIV, their immune system wasn't improving so they kept coming back. It's not one, you know, you are not getting one of these things, you are getting one or two or three of them.

My certain memories and I am sure lots have memories of the night sweats, that was really bad. You know, the night sweats at night, waking up drenched, candida, diarrhoea and things and this was before opportunistic infections really hit in. This was the early days of infection. So, yes, very debilitating and psychologically difficult.

DR WILLIAMS: In terms of things like herpes zoster, which is shingles, as Sian said, become recurrent but the impact of shingles can leave you with very difficult to treat neuropathic pain where which is really debilitating. It is not just the herpes zoster that can be treated, it is the consequences that are really quite impactful.

MS SCOTT: You have mentioned the psychological difficulties. Presumably knowing what is coming, what this means, adds to the burden tremendously to those that were suffering it.

PROFESSOR ANDERSON: Absolutely, yes.
MS SCOTT: I was going to move on now to the AIDS itself.
SIR BRIAN LANGSTAFF: It sounds like something that we had better deal with at 12 o'clock, I think. 12 o'clock.
(11.30 am)
(A short break)
(12.04 pm)
MS SCOTT: We were going to move on then from the chronic infection, so to the middle stage, to AIDS itself. You have already given some evidence about how you diagnose AIDS.
We were looking at the table of -- a CDC table, where you -- which sets out the clinical category of AIDS-defining illnesses.
You have explained that in order to meet a diagnosis of AIDS in the UK you need to have one of those AIDS-defining illnesses. Is that right?
PROFESSOR ANDERSON: Correct.
MS SCOTT: Can you just say a little about -- in your report you explain that the way that HIV relates to a person's immune system is reliant on three factors: the microbial exposure of the

patient through life, the pathogenicity of organisms encountered, and the degree of immunosuppression of the host. Can you just explain why those three factors impact differently and give people different experiences of HIV going through to AIDS.
PROFESSOR ANDERSON: So I will kick off on that. So from what we have discussed so far, I hope it's become clear that the clinical -- the things that happen to people living with HIV are a consequence of the immune system weakening.
Now, all of us have been exposed to microbes and germs during our lives and many of us have got different exposures depending where in the world we've been or what we've had in our lives, and many of those infections may stay with us and we don't know we've got them and everything's fine until the immune system weakens, and then some of those things that we have been able to keep in check come back and re-emerge.
So, for example, a particularly prominent one might be tuberculosis, and that then might be much more common in a person who has lived in an area where there is a lot of tuberculosis in

the first place, whose immune system becomes weak enough for tuberculosis that may have been around for a while to emerge, and the pathogen itself, the problem that's going to emerge, how powerful it is. So a very powerful pathogen doesn't need so much immunosuppression to appear and it will depend if you have met that pathogen before.
One particular example which we could use perhaps is cerebral toxoplasmosis. Now that is an infection that lives in meat, and actually if you look across the world, people in France, who are used to eating meat that is rare, often have got much higher levels of having met toxoplasmosis in a previous life than other parts of the world. So that's where we're thinking about the microbial exposure.
If you have met toxoplasmosis in the past, then your immune system becomes weak, that is something that is going to come back, with a brain abscess most commonly.
So when -- when -- and I am thinking back now, sometimes people will come with very undifferentiated symptoms, somebody will come with meningitis, which just suggests

inflammation of the brain. So which sort of meningitis is it going to be? Well, where maybe have they lived? What exposure might they have had? How immunosuppressed are they? So those are the sorts of questions that would have guided the diagnostic process, if you like, in trying to work out what's happening.
The more pathogenic things are happening at an earlier stage. And, for example, things -- there's a particular bacteria called microbacterium avium-intracellulare, normally it doesn't do anything much at all to people but once the immune system is so flat, then it can emerge and cause a problem. So that's something you would see probably much later on in the course.
So it's trying to have a balance, as you are thinking this through, of what somebody might have met before, where they are in their immune system spectrum and what sort of pathogen power there is. But of course, by the time somebody's experiencing something from this list here, these are all things that really only happen when the immune system is really weak. They are a way of signalling how weak the immune

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system has become that somebody is able to have this as a problem in their lives, if that sets the scene.

MS SCOTT: Yes.

Henry, can we turn to Table 2, which is at page 33 of the report.

PROFESSOR ANDERSON: I think the other thing I would just say at this point is if we think back, making a diagnosis of what it is that's the problem is absolutely critical here, because if you don't have anti-retroviral drugs to deal with the underlying HIV, then the work has to be done by the drugs you do have to treat whatever infection or tumour it is that is causing the problem. So the work of making a diagnosis is really important and so people would have gone through a lot of different tests and a lot of examinations to try and find out what pathogen it is if you can't deal with the underlying HIV itself.

MS SCOTT: Sorry, Henry, can we go back to the previous page, the page -- yes --

PROFESSOR COOKE: It is worth making the contrast to what we were discussing earlier about some of those more common conditions where there were

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some treatments. Many of these that we're going to go through are very severe conditions for which many treatments didn't exist, certainly in the 80s through to the 90s, and even quite recently. So the diagnosis was crucial but there was often a limitation in what could be offered in terms of intervention.

MS SCOTT: So I understand from your report that there's now effective therapy for HIV and so these kinds of treat -- these kinds of conditions we're going to look at now aren't appearing, in this country in any event.

PROFESSOR COOKE: Much less frequently.

MS SCOTT: The Inquiry has heard evidence of people suffering these conditions and so can we do the same exercise, can we go through the symptoms here caused by the major HIV-associated pathogens and look at how that would have impacted people and the kinds of treatments, if any, that were available and the burden of that treatment on them.

Can we start with candidiasis, please.

PROFESSOR ANDERSON: I think Sian's already alluded to how painful it can be to have thrush in your mouth but if your immune system is even weaker

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then it can spread down into the oesophagus, which is the tube where you are swallowing food. So a very common complaint people would talk about was how difficult it was to swallow, to eat, a feeling of food being stuck, and pain, real pain as you are eating. Then that would be, I guess, a bit more (unclear) but you could actually find thrush getting into the lungs which would make you cough, short of breath. So imagining a sort of layer of fungus going through the hollow tubes in the oesophagus and the bronchi, which really -- pain, discomfort, difficulty breathing, and I think what you said earlier, the impact on appetite and your ability to enjoy food or eat properly.

I don't know if -- Sian, you might want to add to that --

MS EDWARDS: I don't think there's anything to add -- yes, I mean, I think anybody whose -- most people who had AIDS actually had candida, it seemed incredibly common, and of course when people are sick, what you want to do is feed them, and no-one wanted to eat. And, you know, there's many, many reasons, including the virus itself, that people lost weight, but the extent

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of weight loss amongst this group of patients was extreme and debilitating and -- and extraordinarily painful for family members to -- to watch.

PROFESSOR COOKE: And even in -- in the setting of advanced immunosuppression, even a condition like candidiasis can be fatal. So you can have bloodstream infection, which can be fatal, and -- and many of these conditions we'll go through we'll talk about symptoms but in their most advanced conditions can be fatal.

MS SCOTT: When it gets to this stage was there effective medication?

PROFESSOR COOKE: There are usually medications now for this particular condition, candidiasis, that would be effective. We're seeing more resistance these days to some of these medications. But -- generally speaking -- but these are really relatively recent treatments that are available now.

MS SCOTT: Going down the list then, cryptococcal infection.

PROFESSOR ANDERSON: So cryptococcus is most common -- it's a fungus. It most commonly in the context of HIV infection would cause

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meningitis, a particularly nasty meningitis, so meningitis would then often present with -- in this particular case, awful headache, change in conscious level, very debilitating. And one particular feature of cryptococcus is it sort of clogs up -- the fluid round your brain can't flow properly down and away. So people often would get hydrocephalus and -- and very complex meningitis from a cryptococcal infection.

PROFESSOR TUDOR-WILLIAMS: The treatment required repetitive lumbar punctures to decrease the pressure, which was highly invasive and discomforting.

DR WILLIAMS: And the consequence if you didn't do that properly was blindness. People would lose their sight. So cryptococcal infection is one of the most severe opportunistic infections we see, with a high mortality. Getting it early was very important. People presenting late had -- you know, their outcome was in the early days was not very good.

PROFESSOR ANDERSON: I would also add the early -- the treatments for fungal infections, they have advanced a lot but the sorts of treatment we might have had available when we were seeing

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a lot of -- they were really unpleasant for terosin, very toxic treatments. So even if there was an anti-fungal agent that you might want to use, it would have been very unpleasant.

PROFESSOR TUDOR-WILLIAMS: It's also a really good example of a pathogen that's prevalent in the community. You didn't have to go further than a London park because pigeons, and pigeon poo particularly, was implicated in the spread of cryptococcosis, and again it comes back to the idea that probably all of us in this room who have ever walked through a London park have got exposed to cryptococcus but if your immune system is working okay it doesn't cause any problems but if your immune system is damaged it causes this really debilitating meningitis.

MS SCOTT: I daren't try and pronounce the next one down. Does somebody else --

PROFESSOR ANDERSON: Cryptosporidiosis.

MS SCOTT: -- Want to have a go?

DR WILLIAMS: Cryptosporidiosis.

MS SCOTT: Can somebody speak to that?

PROFESSOR ANDERSON: Well, again, it's another one of those infections that really indicates very, very profound immunosuppression, and it's --

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again, as Gareth has said, it's a thing that's knocking around in water supplies in any event, but we would see it in the context of HIV, often really debilitating, causing terrible, terrible diarrhea, very watery diarrhoea, which was sometimes with a crampy abdominal pain, but the cardinal feature was that people lost a huge amount of weight and fluid and -- and really, really intractable diarrhoea. And I think the most serious issues around cryptosporidial diarrhoea were really profound. And it was a horrid -- horrible infection to have.

MS SCOTT: Do you want to add anything to that?

MS EDWARDS: It -- I think it's -- this was the -- I'm actually sitting here listening to this and memories are coming back. And I was a nurse so I can't imagine what people out there are feeling. I'm -- going through these is quite I think possibly quite traumatic because I think our memories of how people -- because, as I said earlier, it isn't one: people had candidiasis and they had cryptosporidiosis, you know, and they had something else. And these -- these -- it is a ruthless -- in some countries it's a ruthless disease, and the impact of --

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certainly of cryptosporidiosis from a nursing and medical point of view to try and control this intractable diarrhoea meant that people couldn't go out, they couldn't leave the toilet. It was a dreadful, dreadful disease, which was very difficult from a medical point of view to control. And again, the families, it was a very hard thing to watch and care for people who had this condition, which was again common.

PROFESSOR TUDOR-WILLIAMS: And we really didn't have useful treatment.

PROFESSOR COOKE: Probably it's the best example of where we still really don't, and the thing that's transformed what we can do is the advent of HIV treatment itself. We still have very poor treatment for cryptosporidiosis and we desperately need it.

MS SCOTT: CMV?

PROFESSOR ANDERSON: Where shall we start? CMV. Goodness.

Graham?

PROFESSOR COOKE: So CMV is a viral infection. It belongs to a similar family to glandular fever and many people are exposed to it from early in life and increasingly exposed particularly

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through adolescence and early adulthood.

Again, it's an infection that many of us handle without any great problem if our immune systems are good but in the setting of progressive weakening of the immune system, that virus can reactivate, and it's the reactivation of that virus that can be very debilitating.

And often with advanced infection one of the more common thing we used to see, and thankfully see much less of, is -- was damage to the back of the eye, which can really affect vision. It's a good example of something that could then be long-term, even with effective treatment and recovery of the immune system subsequently.

You can see reactivation in other parts of the body where it can also have very devastating effects in terms of the gut, and you can have a very inflamed gut, colon, and diarrhoea which can be very hard to treat and painful, reactivation at the upper end of the gut, in the oesophagus, where it can be very painful, and then reactivation in the lung as well where it -- a bit like pneumonia but you can have inflammation in the lung which can make

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breathing difficult and getting oxygen in.

It is an example where we actually have got much better treatment now but some of those earlier treatments that we used were very toxic, and so, again, it's the sort of recurring theme of individuals who had very advanced HIV, were very sick, with really the only options for treatment being very toxic medications which we were obliged to use really.

PROFESSOR ANDERSON: And because of the toxicity to the veins, we often used to have to implant what were called port-a-caths. So a person might have an in-dwelling venous access which would often be on the chest wall so that the drug could go into a big vein because it would be too damaging to the veins to go into the arm, and so often people would have to have a surgical procedure to have a thing called a port-a-cath fitted. And then that needed to be looked after and managed as well as getting the medication in as well. So it was really complicated.

PROFESSOR TUDOR-WILLIAMS: Also cytomegalovirus is a really big issue for pregnant women. So in the context of HIV, that was a co-infection that we saw really too commonly in the infants born

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to mothers who were HIV infected. And I just remember treating far too many children who had gone blind as a result of HIV and CMV co-infection.

And -- and I'm sure you remember that in the London Lighthouse, there may be people in this room who were involved in planting a garden that was full of different sensory plants with really lovely aromas because of -- because retinitis had blinded quite a number of people who were in-patients at the London Lighthouse. And I always remember thinking that was a tremendously wonderful humane response to what was a terrible co-infection.

DR WILLIAMS: I think this is really -- the impact of CMV in the eye, you -- they would get -- one episode was treated, they would have to remain on treatments to try to prevent relapse, but then they -- ultimately they would then get other another relapse, and at each relapse there would be loss of vision. And so many people who developed CMV retinitis before they died they were -- they went completely blind. It was a really debilitating, horrible thing.

MS SCOTT: Encephalitis?

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PROFESSOR COOKE: Not much better. So -- so HIV we know can directly affect the brain both in acute infection and chronic infection, and that can lead to quite a significant clinical manifestation of confusion or even more progressive cognitive sort of challenges with thinking and memory and so forth, which in advanced HIV could -- could be very profound. And even with the advent of effective HIV therapy, not always reversible. So it is still an issue that we have to contend with in clinics today, often to a milder degree thankfully but nonetheless still something that is sort of an active area of interest in particular.

MS SCOTT: You touched on herpes zoster earlier. Here we have herpes simplex. Is there anything you want to add to that?

PROFESSOR ANDERSON: Herpes simplex is an infection the skin, of the genitals, of the mucus membranes. You don't have to have had chicken pox to get it. So zoster is related to the chicken pox virus but herpes simplex -- many people have it and it doesn't cause problems, again, until the immune system becomes weak. But it's one of the ones that's quite a powerful

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pathogen. So, again, it would come quite early, and I think the level of painful ulceration -- and, again, if you've got some oral candida and herpes simplex in the mouth, exquisitely -- really painful and -- and very difficult, often, to manage. So, again, it would be one of the things that we did have some treatments which you might then ask somebody to take long-term to try and keep it under control. So, again, adding another layer of medication, both to treat and to try and prevent recurrence.

MS SCOTT: Histoplasmosis.

PROFESSOR COOKE: So it's another relatively unusual infection in this case but, again, really we do see occasionally in people who have healthy immune systems but relatively rarely, but when it -- when it did affect people with advanced HIV -- we don't see it very often these days at all, and now fortunately we have better treatments for it, but it was a condition that had a very bad outcome in the setting of some of the treatments we had available at that time, and these anti-fungal drugs we have already mentioned were often, when they were available, quite difficult to -- to take and -- and to use.

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And so -- yeah, so fortunately a condition that we see much less of but nonetheless often very serious, if not fatal.

MS SCOTT: Kaposi's sarcoma. That's something you've said in your report is not something that's seen very much in this -- in those that are infected through blood and blood products. Is it seen in that cohort of patients?

MS EDWARDS: It depends on the lifestyle.

PROFESSOR ANDERSON: It depends whether people have been exposed -- again, it has a viral origin. It's related to some of the other herpes viruses so it can present itself, but it is much less common, but when it happens, it -- it's on the skin, it's very prominent often. People have lesions that appear that are very easy to see and can get into the gut and into the lungs and cause severe systemic problems as well.

MS EDWARDS: It is, of course, the early look of AIDS that many films are based on with people who have these purple blotches all over their bodies and skin, and was deeply stigmatising for people. And if there was any way -- with some of these things you were able not to be known as having HIV infection and AIDS; if you had

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Kaposi's sarcoma, there's no way.

SIR BRIAN LANGSTAFF: If my understanding is right, then it was Kaposi's sarcoma that was a particular identifier of the five adults who gave rise to the first report in the western world of AIDS.

PROFESSOR ANDERSON: Indeed.

SIR BRIAN LANGSTAFF: I think -- am I right in thinking that it was because of a specific drug that was really only used for that that the CDC was able to investigate why that drug was being used so much in that particular --

PROFESSOR ANDERSON: That was pneumocystis, the next one along.

MS EDWARDS: But they came together.

PROFESSOR ANDERSON: They came at the same time and people would often have both.

SIR BRIAN LANGSTAFF: Thank you.

MS SCOTT: Lymphoma?

PROFESSOR ANDERSON: Lymphoma, where shall we start? Lymphoma is a cancer, it's a cancer that has probably -- it's got an infectious aetiology but again we're seeing it much more commonly. These are cancers that can occur in people without HIV but much more common with HIV, and

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the fact I think -- that the CNS, the brain -- the lymphoma that affected the brain particularly relates to co-infection with HIV.

Hard to treat and, again, going back to some of the chemotherapeutic approaches, some of the oncology approaches, often -- it was often fatal.

DR WILLIAMS: The other thing about lymphomas, lymphomas are seen in people who have other immunosuppression. So it's people who have had transplants who get a much higher risk of lymphoma. I mean, really, there is lymphoma -- when it presented, it usually presented with advanced lymphoma rather than early, and therefore the outcome of treatment was often very difficult -- you know, it was very much worse.

But lymphoma -- now, treatment of lymphoma in someone who is HIV positive, the outcome is no different to someone who is HIV negative. There has been, you know, a marked improvement in that.

MS SCOTT: Can I just invite you to look down the rest of that list. Are there any of those symptoms or pathogens that were particularly

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prevalent for those that have been affected by bleeding or blood disorders or -- that you would like to talk to because of the burden of treatment or the burden of the condition?

PROFESSOR ANDERSON: I think we have to include pneumocystis here because that was probably one of the most common AIDS-defining conditions, and that is the one that you are referring to. A lung infection most commonly, although it could affect other parts, and often very slow to present itself. So quite a long time feeling short of breath, bit of a cough, not necessarily that much to see but actually by the time people came to medical attention often very short of breath, feeling very -- it was a very uncomfortable sensation, not bring able to breathe and shortness of breath on exertion. And it -- one -- perhaps one of the commonest opportunistic -- and earliest.

PROFESSOR TUDOR-WILLIAMS: Rather than affecting the lung airway, it was affecting the lung tissue and preventing gas exchange so that certainly the children I looked after had very profound low levels of oxygen, which makes you feel horrible, and it was all part of that systemic

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illness.

PROFESSOR ANDERSON: Yes. What I would say is that we quite -- even before we had very effective anti-retroviral therapy it became quite clear that taking regular low doses of an antibiotic called septrin could actually help prevent this occurring, and so, again, another drug that you might add in not to deal with the HIV but to try and prevent this particular infection, but would add to the burden of medications that people might be taking. And people with HIV often had high levels of allergies to drugs, and septrin in particular would be something -- people would start septrin and come out in a rash and have a drug reaction, as well as everything else.

MS SCOTT: The oral evidence the Inquiry has received from some of the people who experienced some of these conditions and then recovered and are alive today is that they suffered ongoing damage as a result of these conditions. So, despite having been cured, they continue to exhibit symptoms. Is that right?

PROFESSOR COOKE: I think that's particularly true for a couple of the conditions we haven't dealt

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with, so progressive multifocal leukoencephalopathy and toxoplasmosis are both conditions that affect the brain, caused by different pathogens that reactivate in advanced immunosuppression. But I -- you know, I still have patients in my clinic who are now relatively well, with -- with (unclear) vent strokes from conditions like this, so very profound long-term disability that can result even when HIV can be treated.

PROFESSOR ANDERSON: Yes, so CMV, cryptococcus, toxoplasmosis, would all have long-term, lasting sequelae, even if the acute episode had been dealt with.

MS EDWARDS: It may be just worth noting, as Jane said, each of these things it's not one, it's many, and for all of them there are treatments that are being tried and trials that are being tried on some of these infections in these early days but the treatments themselves were often very, very difficult, so there were further treatments, like anti-nausea treatments and such like to counteract the side effects of treatments. So it's just to sort of put in to perspective that people are very sick with

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multiple infections, with multiple treatments, and side effects and constant, and so the amount of treatments that people were taking was extraordinary.

PROFESSOR ANDERSON: Following on from that as well, the numbers of times people would be in hospital. So this would, you know, you have -- something would happen, you come into hospital, you would have an episode of treatment, go home, confirm back with something else. So there was a lot of people coming back and forth, as well as the treatment they were on, but hospitals as places of people coming back and forth to much more regularly.

DR WILLIAMS: People might present with pneumocystis and you might be able to prevent that again but then they may then present with cytomegalovirus retinitis and you need treatment for that to prevent that and then they might present with toxoplasmosis and stroke and then lastly present with MEI, so there was a series of very severe opportunist infections that required preventative therapy and treatment but also very debilitating.

MS SCOTT: You have also in your report drawn

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attention to the fact that there are other health complications which are observed in those that suffer from HIV. I am talking at page 25. So other than AIDS-defining illnesses, you observe that there are other health complications that are observed and one of the ones that you draw attention to is epilepsy, which can develop independently of HIV but also be caused to be linked to it.

Can you tell us a little bit about that. It's the second paragraph down in page 25.

PROFESSOR ANDERSON: So epilepsy is a seizure disorder and there can be multiple causes of seizures, so I think what we're trying to draw attention to here is that there are many of the clinical editions we have been discussing here which would be related to seizures, cryptococcal meningitis, toxoplasmosis, lymphoma, could all have an element of seizure activity around them and somebody may also have epilepsy, idiopathic epilepsy, as well or separately. So I think that the sense that we're trying to draw attention to here is you may find some of these sorts of disorders in parallel.

PROFESSOR COOKE: I think it is worth clarifying for

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epilepsy that really we think of it, as you say, as a consequence of brain infection and a focus of brain infection generally in the HIV positive population.

Clearly anyone can get epilepsy and it's relatively common in the general population but in the absence of an aggressive brain infection then it's relatively uncommon. Probably wouldn't be of greatly increased prevalence.

PROFESSOR TUDOR-WILLIAMS: Certainly from a paediatric perspective, and I think it's true in adults, that HIV per se, the encephalopathy associated with the HIV virus did not cause seizures. It usually suggested there was something else going on. That was one of the problems, that you then do a CT or -- I can't remember when we started doing MRI scans, but you will see a lesion inside the brain that would be the likely cause but you didn't know whether that was lymphoma or toxoplasmosis and you'd take an educated guess and you'd treat the toxo and if it didn't go away then you presumed that it was probably lymphoma.

I mean, it was not -- it doesn't lend itself to doing biopsies and getting tissue

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diagnoses. It was a really big diagnostic challenge back in the early '90s.

DR WILLIAMS: I am not sure if we are going to go on to it later but the other important things, these are the AIDS-defining conditions, but there are other HIV associated co-morbidities which became much more apparent as treatment became more effective. I don't know whether you wanted to --

MS SCOTT: Yes, now would be a good time. That was my next question. Can you tell us about that.

PROFESSOR ANDERSON: We're now in the position that if you can with anti-retrovirals ensure that the immune system remains strong enough for the things we have been discussing just now to not occur, then there is time for other things to begin to emerge, which in the early days we didn't necessarily see because people died of some of the things we're talking about now.

It's clear, I think one of the things that Ian referred to earlier, is that with HIV the body's in a constant state of inflammation, if you like. There's an excessive amount of inflammatory response going on. That seems to predispose to higher rates of cardiovascular

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disease, some of the metabolic disorders, bone disease, so there's a link between viral activity and inflammation.

On top of that, we know that there are some behavioural aspects. So more people living with HIV tend to smoke, and that may predispose to some of these other -- there may be some lifestyle issues as well and we also know that the medications that are used in the treatment of HIV and its complications can themselves precipitate -- particularly, bone disorders are particularly common, so we see more long-term chronic conditions now because people are alive and this sort of low grade inflammatory response is continuing.

DR WILLIAMS: Treatment is very effective in terms of getting the immune system better but there's still ongoing background of inflammation and that inflammation is thought to drive some of these increases in risk of other chronic diseases of ageing such as kidney disease, such as heart disease, such as liver disease and cancer, so we are seeing far more increase in non-AIDS defining cancers, like lung cancer is more common in people, skin cancers, and cancer

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is now by far the leading cause of death or mortality in someone with HIV not the AIDS-defining conditions.

Equally, if you look at cardiovascular disease, HIV is thought to be equivalent to smoking in terms of risk of cardiovascular disease, to give you a sense of the risk.

MS SCOTT: The increased risk of these other health complications is increased as against the HIV-negative population.

DR WILLIAMS: Yes, absolutely. So yes we've dealt with very effectively in terms of improving the immune system but we're left with a population where they have a much more increased risk of other chronic diseases of ageing compared to the HIV negative population. So although life expectancy has improved this is often associated with increased frailty and impact of quality of life.

MS SCOTT: Do you know what the increased risk is? I know it's on a population level but increased risk as against those that don't have HIV?

DR WILLIAMS: In terms of, for example, cardiovascular disease then there's a sort of -- it's the same as if you were a smoker so if you

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are a smoker then your risk of cardiovascular disease goes up. In chronic kidney disease your rate of decline in renal function is faster than in someone who is HIV negative.

MS SCOTT: So you have set out the burden, if I can put it that way, of the virus itself, the AIDS-defining illnesses and the invasive treatments for those particularly in the '80s and '90s, the treatment for the medication for the ART, anti-retroviral medication, and these other associated health conditions. Can we talk now then about, and we've touched on this, the psychological impacts of having HIV and AIDS and again we've touched on the stigma of that as well.

DR JOHNSTON: I think in the community for people to live with HIV, if we remember back, and I often think of the adverts that were on at that time, there was a huge stigma associated with it. I think if we think perhaps of the corona virus now and then think of the people who get corona virus being somehow stigmatised. It's that sort of thing. So there was a huge stigma attached to that.

Dealing with a chronic life-shortening

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illness obviously has psychological impact and then you add to that dealing with the putting a stone in a pond the ripples, so you are dealing with your family, you are dealing with the lack of support, the lack of perceived sympathy from the wider population sometimes, and against the background of almost national hysteria. So all the elements were there I think to really make for a very psychologically damaging and difficult time and all of that enhanced the stigma that was associated with it.

MS EDWARDS: Just to add, and I think Gareth can do this better than me, but of course the people we are dealing with are often children and adolescents who were going through, as we were talking about on Tuesday, huge changes in their own lives and separation which should have been a healthy separation from families, parents and trying to build their lives and their futures which, when we have just described what some people were going through, was near to impossible and also created great dependency, of course, on the family. Maybe Gareth can talk more about that.

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It's really important that we think that many of us dealt lots with adults who are infected but there is a high proportion of these young people, children and 16/15-year olds.

PROFESSOR TUDOR-WILLIAMS: I like David's analogy of the ripples spreading outwards. Certainly we've seen -- we're always at pains to point out if a child was not infected, were they okay? No they were affected by what was going on within the family so, yes, it's a very real issue.

DR WILLIAMS: I think we really can't overestimate the impact of psychological problems in somebody who is HIV positive. It really is something that is core and runs through the whole life of someone who is HIV positive. Some people will adjust to that diagnosis quite quickly. Others take a long time to adjust to that.

Even in surveys of positive voices, a survey produced by Public Health England, even now looking at the incidence of mental health disorders, it is 30 per cent in the patient population with HIV compared to only a few per cent in HIV negative population, so I really cannot overestimate the impact of mental health problems.

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PROFESSOR ANDERSON: Absolutely.
MS EDWARDS: Sorry, I was just going to say one other thing and I think that that is the issue of stigma, which again we talked about on Tuesday in great depth and mentioned is that people hid away. Most people when you have ill-health you see your doctor, your nurse, your community, and you are able to share this pain whether it be physical or psychological and you get support and people care and sympathise, and HIV is unusual and awful because of the fact that so many people were unable to do that sharing and often lived in isolated communities and were unable to share what they were going through and the psychological burden on not being able to share the pain psychologically or physically going is huge for people.
PROFESSOR ANDERSON: That in the next, now we're down to that, the sense that the fear that you might transmit or pass the HIV on to somebody else might actually make people go into themselves even more and avoid forming new relationships and so becoming even further isolated.
MS SCOTT: The impact of going through those

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psychological and emotional processes while one is physically unwell, what is the impact on one's physical health of those mental psychological and emotional difficulties?
DR JOHNSTON: Sorry, just before we go on to that I would also say for the wider family members, because quite often people who had HIV and subsequently AIDS and would have been seen at that time as having a terminal diagnosis came home to die and they often came to more isolated communities or where there was even more stigma attached and those people subsequently died and it left a huge impact on their family.

So not just for the people who had the illness but for the family and I think that continues to this day. I certainly know of families where they have lost a loved one and that still has a huge impact. So sorry then to return to your specific question, I mean, the whole gambit of mental illness, obviously depression, I think of cases of self-harm, right up to suicide, absolutely, and again I think for the whole family circle because people did feel a lack of support, perceived a lack of support, I think healthcare professionals sometimes we

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felt powerless and that may have transmitted to people feeling that we, even in extreme cases, didn't care but sometimes it was the lack of support and because people didn't neatly fit into a particular area where they could be referred for treatment or whatever, so you might have been depressed but then you were referred maybe to mental health services but it was sort of thought, well, this person has HIV or AIDS so that's obviously the cause of that and that was sort of almost compartmentalised.

Again, an actual lack of support and a perceived lack of support meant that those mental health outcomes were perhaps worse.
MS EDWARDS: I think one other thing as a community nurse, I think I have to acknowledge the fact that we were attached to big specialist centres often and where that did exist sometimes the care and support was there and we were able to help people to an extent, but outside those specialist centres and to the more rural regional -- I'm using my Australian terms now -- the regional areas of the UK, sometimes the support and the medicine and the doctors were not there. They just were not. The ones that

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were there may not have had the education and the knowledge and so people were let down and so they had to survive in a family unit often alone with very little support.
DR JOHNSTON: I think it is important to remember this was the pre-internet age which, of course, has revolutionised and people can keep in contact with self-help groups and other people who are suffering in a similar way. People really did feel very isolated at that time.
PROFESSOR ANDERSON: I think there's also, this is still, there is some truth in what you are saying today. We know, as Ian's alluded to, that the burden of mental ill health is higher amongst people with HIV.

Actually, many of the specialist centres, we ensure that we have psychologists on the team. We have very, very close working relationships with our mental health colleagues, but those may not be available outside those HIV specialist centres, even today. So we know the pressure on mental health services in general means that there is still unmet need and so even in an era of anti-retroviral therapy we are still seeing poor mental health and still seeing

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unmet need for its improvement.

PROFESSOR COOKE: That was an issue that came up after yesterday as well in that, as you say, we still have limited access to mental health support for payments with HIV but actually it's probably better than for patients who have mono-infection with viral hepatitis where often there isn't even funding for psychological support services. Sometimes people can access that through HIV services where it's available but it's still a big issue in terms of accessing that.

MS SCOTT: Professor Anderson, I know you were involved in a study in 2004 which looked at stigma in a population in North London. One of the findings from that report was that a lot of the participants were reporting that they had been discriminated against within the Health Service itself and they reported discriminatory behaviour as a result of their HIV status from GPs, from dentists, and from hospital workers outside HIV.

I just wondered if that is something that patients have reported to the panel and what challenges and consequences arise for patients

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and for those trying to care for them.

PROFESSOR ANDERSON: So the study you are alluding to, we carried out, a group of us carried out a questionnaire-based study for people who were living with HIV attending clinical services in north-east London particularly. It was asking a whole array of questions about what life was like and the challenges that people were facing but the particular question I think that you are alluding to, we asked a particular question, "Have you experienced discrimination consequent upon your HIV infection?"

The thing we have to say is this was a questionnaire-based study, so people were ticking a box. We weren't interviewing people like Sian was describing yesterday, so it is a subjective response to a question with a tick box, "Have you felt that experience?" A very high proportion of people said that they had. Digging into that, you are absolutely right, it was an array of healthcare workers amongst others. I mean, it wasn't exclusively there, it was within a greater societal picture.

I think the thing that comes from that was that the people who had been living with HIV for

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the longest experienced the highest risk of experiencing discrimination, often because they had been through more episodes of care or they had longer time living with HIV for that to have happened.

The question was quite specifically asked, "Do you feel that this was a result of your HIV infection?" and people's answer to that was yes. I think there have been strides made. We did the study in 2004. We wrote it up in 2008 but, as Ian has alluded to, we have the positive voices survey, which, the most recent iteration was 2015/16 and still we're seeing, okay, the proportion has gone down slightly but we're still seeing people who are afraid to access healthcare because of the response that they may have. Ours was the first quantitative study to actually demonstrate this happening.

Again, it has led to a whole array of attempts going, "What do we do? How do we move this forward", because it's unacceptable and every possible which way, and again going back to Ian's point about long-term conditions, more people with HIV are meeting more healthcare practitioners in more settings, so it's

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absolutely crucial that we address this.

PROFESSOR TUDOR-WILLIAMS: I think also just remembering back the difficulties that we had persuading parents that their children's best interests were served by their GPs knowing. There was a great deal of resistance to the idea of general practitioners being informed about the HIV diagnosis.

That was partly driven by experience that, I don't know whether David can attest to this, but we would get reports back from the families saying their notes and their children's notes would have a big red spot or something to identify them as HIV infected.

It was vaguely covert in that it wasn't actually written HIV but it was -- everybody in the practice knew and they didn't want to experience that. They didn't want their children to experience that and the other element was in the school system as well, that, you know, there were sometimes advantages in the school understanding why the child was missing a lot of school because of hospital appointments and in-patient care episodes. But then, you know, there was an issue about the transfer of

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that knowledge from primary education into secondary education, without anybody thinking to ask the family and the child in particular whether they agreed with that. It was a really big issue for us.

DR JOHNSTON: I think that's absolutely true and I think in primary care there would have been a concern that people were stigmatised at one end of the spectrum. I think at the other end of the spectrum people didn't want it recorded on their notes because it did have implications for life insurance and, you know, getting a mortgage and all sorts of things like that, in terms of school, you know, I've certainly experience of kids being asked not to take part in sport because, you know, there was some risk of something and just again the whole stigma that, you know, general practice, may be a smaller community and though, of course, confidentiality is at the heart of everything that we try to do, there is always just that concern that some information might become known. So absolutely I think that's a valid point.

MS EDWARDS: At the same time as Jane was doing the

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quantitative data, we were collecting qualitative data from people with haemophilia and HIV, as I have mentioned the other day, and then secondly their families.

I think what's just to add on to that, that I've recently done a same situation life history with healthcare workers and I just on this subject I talked to a number of community HIV specialists. Their job was to refer to GPs and services in the community outside of the hospitals that they had been treated so that they could go home and many of those nurses who were trying to make those referrals came to huge resistance from many services who didn't want to take on board the care of the patient with HIV infection and that, of course, also things like undertakers, you know, people who struggled with trying to get their partner being taken away who had died and the resistance of undertakers.

It was widespread discrimination across the board and, like we keep saying, there were some very specialist centres where people even today, people walk into a clinic that I work in because it is a sexual health clinic and they say, "when I walk through this door I feel safe,

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but out there I never feel safe". I think that's today, so ...

MS SCOTT: Professor Anderson, you touched on this, the consequence of that to those who are infected and affected not only is psychological and emotional but a reluctance to access healthcare services, so a direct impact on their physical health.

PROFESSOR ANDERSON: Absolutely, no question. Even today I can think of a woman who said, "Oh, I've been called for a mammogram but I just don't want to go because they are going to start asking about my HIV. I think I won't go".

MS SCOTT: Before we break for lunch can I just pick up a few questions about co-infection. We covered some of it yesterday, co-infection with hepatitis, covered some of it yesterday and I don't want to go back over that but that was primarily from the point of view of hepatitis but from what I've understood, co-infection with hepatitis B or C when one has HIV, doesn't alter the natural course of the -- doesn't alter the way the HIV develops. It's really, the alteration is all on the hepatitis.

PROFESSOR COOKE: In general, yes, that's correct.

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MS SCOTT: What I would like to ask you is the difficulties of managing the two infections together, so whether it's hepatitis B and HIV or hepatitis C and HIV.

Are there difficulties in taking medication for both infections at the same time?

PROFESSOR COOKE: So certainly that is true and I think we touched on some of that yesterday. It's slightly different issues, depending on whether you are infected with HIV and hepatitis C or HIV and hepatitis B but we talked at length yesterday about interferon and the challenges of taking interferon. We know that for individuals infected with HIV, particularly those with advanced immunosuppression, who needed hepatitis C treatment, the treatment was more difficult, it was more prolonged and it was less likely to work, so all of those factors combined alongside the additional toxicity that you might have taking those medications with medications for HIV were huge challenges which were a barrier to both starting care and having successful treatment for hepatitis C.

We know that without effective HIV treatment that hepatitis C progresses more

quickly and the incidence of serious liver disease is higher. That has changed in recent years but it was certainly the case for a very long time.

Similarly, for hepatitis B we know progression was more aggressive. Until relatively recently we didn't have specific treatments for hepatitis B that could be taken easily with HIV treatment. That's improved slightly with the advent of some medications which were active against both viruses but we still have a few patients who require different sets of medications for their HIV and hepatitis B.

So certainly additional challenges and particularly around the additional toxicities of drugs that were being used.

MS SCOTT: The choice for the patient is whether or not to take the medication for the hepatitis, rather than whether or not to take the medication for the HIV, if I can put it that way.

PROFESSOR COOKE: Yes, that's changed over time and I think that that balance of, in particular, so obviously these days we have not really touched

on this yet but we would be recommending everybody with HIV to be on treatment. That wasn't always the case but, by and large, by the late '80s early '90s most patients would be on some treatment which would be quite toxic. The decision of whether to take hepatitis C treatment would be a balance of how likely it was to be effective, balanced against the toxicity risks of taking it and, yes, so that would have been an issue, particularly before the advent of highly active anti-retroviral therapy.

MS SCOTT: To reassure you I am going to be asking questions about treatment for HIV after lunch. Is there anything anyone wants to add to that discussion?

SIR BRIAN LANGSTAFF: That brings us neatly I think to our lunch break. Two o'clock, please.

(1.00 pm)

(Luncheon Adjournment)

(2.00 am)

SIR BRIAN LANGSTAFF: Yes, Ms Scott.

MS SCOTT: As promised before lunch, I am going to turn to treatment but before I do, I just want to make a comment really by way of explanation

both to the panel and to those that are listening, particularly for those that weren't here yesterday, and that's just to say that in your report you were asked to and have provided a short chronology of key events, and consistent with the approach that has been taken with other expert groups I am not going to ask you what was or should have been known by clinicians during the first half of the 1980s about risks of HIV or HTLV-3 or AIDS, or -- and I am not going ask you about medical and scientific work being done then in relation to the virus or to the development of a test for what we now know as HIV.

The reason for that is because it is a question of fact for the Inquiry, which the Inquiry is investigating by reference to contemporaneous material, and so those questions -- any questions in relation to that will not form part of what happens for the rest of this afternoon.

SIR BRIAN LANGSTAFF: And, I should add, by -- in relation to the evidence of those who can give their own contemporaneous testimony.

MS SCOTT: Indeed.

Moving, then, on to the treatment for HIV itself, we've touched on treatment for some of the AIDS-defining conditions, but moving on to the treatment for HIV itself, can somebody give us a brief outline of the first generation treatments, the mono-therapies.

DR WILLIAMS: The first therapies basically targeted a particular enzyme in the virus replication cycle called reverse transcriptase. So reverse transcriptase was responsible for manufacturing a double-stranded DNA copy from a single-stranded RNA copy in the infected T cell. So it's an enzyme that was encoded by the virus to be able to do that. So what -- the initial first generation drugs, the nucleoside reverse transcriptase inhibitors targeted that drug -- targeted that enzyme by basically binding to the active site of that enzyme and inserting into the elongating DNA chain and terminating it. Right? So that's the way it worked.

Now, the first drugs were a drug like AZT, or azidothymidine, now called zidovudine, which was not -- wasn't developed specifically for HIV but came off-the-shelf. It was actually

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a previous drug that had been tested for cancer but it did -- had been known to have an effect on -- on reverse -- on this -- what was -- being able to stop the reverse transcriptase enzyme.

So that was originally made available in the UK in mid-1987 following the results of a trial in the United States which looked at giving patients who already had AIDS or severe disease zidovudine, and the trial was stopped after a few months because there was a much higher mortality in those who didn't -- who didn't receive the drug compared to those who did.

So the death -- mortality fell from 14 per cent down to 1 per cent. In fact, there were 19 deaths in the -- in the control arm and only one death in then -- based off that, zidovudine was licenced, right, as something that would be able to reduce or improve mortality.

The problem with zidovudine mono-therapy is that at the time we didn't have the same knowledge of the virus as we do now, but it became apparent that the clinical benefit of that was short-lived. And it came at a high

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cost of toxicity in terms of side effects. The dose that was used in the early trials was twice the dose that is now licensed for it to be used, and so, yes, there was a desperate need to try and develop drugs and get treatments out there, and -- and this was made available, but it was by far -- you know, it was a drug that really was not fit for purpose in terms of being able to deliver what we wanted to achieve.

There were other nucleoside reverse transcriptase inhibitors that became available in the early 1990s. That included zalcitabine, or DDC, or didanosine, DDI, and stavudine, D4T. They all worked in the same way, in that they basically inhibited this enzyme in the -- the virus needed to be able to infect a T cell and for it to replicate itself within the activated T cell. All these D drugs, as they were shown, equally had side effects that were quite marked and quite severe. So, for example, zalcitabine was a drug that had a high level of neuropathy, causes a toxic neuropathy in about 30 per cent of patients. Stavudine did the same. DDI was very difficult to take. It was, first of all, available as a powder, then became quite

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a chalky big tablet, before it became a capsule. So they were -- they were drugs that were developed in response to a crisis, in terms of trying to find something that would work, but they were drugs that were really quite -- had high level of side effects.

MS SCOTT: Henry, can I ask you to turn to page 51 of the report. It is probably 52 of the document. There's a table, table 4 there. Yes, so it's the page before that.

The Inquiry has received a lot of evidence from people that took AZT in particular in the 80s. You've created a table there that sets out some of the common side effects:

"Blood disorders: anaemia, neutropaenia, nausea, vomiting, diarrhea, abdominal pain, headache, malaise, dizziness, myalgia, and lipoatrophy."

Does anyone -- can anyone else add anything about -- in particular in relation to AZT but all of those first generation medications that you have just spoken to, about the burden of the side effects and the difficulties that Dr Williams has raised about how difficult they were to actually take as

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a medication.

PROFESSOR ANDERSON: Can I just add something there, and I think that my very strong memory of AZT -- at the beginning -- I think you were right -- the dosing was very high, it caused anaemia in a lot of people, and it got to the point actually where some people were blood transfusion dependent. So we used to have people who would take their AZT and then come in to have blood transfusions to deal with the anaemia that was the side effect of the drug.

So given there wasn't anything else on the market, we were managing side effects, really serious, serious side effects, in order to try and continue to -- this drug. But we also had timers, I remember people used to get up in the middle of the night to take a dose, which was incredibly disruptive. So as well as feeling terrible, it really had a lot of implications for life, for how you lived your life.

PROFESSOR COOKE: A lot of those side effects, as we have heard, were very common and very severe, and some of those very long-lasting. So, for those fortunate enough to survive, and still some of those patients in clinic now will still

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have some of those side effects as a result. So peripheral neuropathy for example. And there's a condition listed here which is a bit like cirrhosis which we see in a small number of patient who had didanosine, that is still an issue today, so many of these things ...

PROFESSOR TUDOR-WILLIAMS: But can I just put the counter-argument, that the -- trials of the use of zidovudine, AZT, to prevent or decrease the risk of transmission from mothers to their babies was extraordinarily successful. I mean, really ground-breaking work, and it is still used today. I mean, we still use zidovudine to protect newborn infants to reduce the risk of transmission of HIV. So it's not -- whilst you read these lists of toxicities -- and indeed in the beginning I remember we were -- that very first child I looked after in 1988 we put onto continuous infusion of zidovudine, round the clock, 24 hours a day, because we knew so little about how the drug was distributed. But I wouldn't want to leave everybody with the impression that this is a -- such a toxic drug that it has no place in modern medicine, because it is still being used today.

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PROFESSOR ANDERSON: The caveat to that, of course, is we have learnt, and -- and so the doses that we are using are much lower, and we are able I think, now, to manage that drug in a useful way, whereas at the time Ian's described I think we hadn't got that knowledge of how to best use the benefits it could bring, and so we saw quite a lot of toxicity.

PROFESSOR COOKE: But over -- saying, further, that there may be people -- and we still have patients who are still on it --

PROFESSOR ANDERSON: Absolutely.

PROFESSOR COOKE: -- and there is a minority of patients who don't get the side effects, and if they have been on the treatment for a very long time, it may still be an appropriate treatment to be on.

DR WILLIAMS: And I think it's important -- this is desperate times in terms of people trying to find something that would stop the progression to AIDS and to -- for people dying, and so people would take medications in the hope that that would buy them some time in the way that people might take cancer chemotherapy to buy them some time.

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So -- but -- yeah, I mean, undoubtedly particularly -- you know, studied DDI and zalcitabine were all associated with quite severe major side effects. They are no longer particularly used these days. They were -- in fact, zalcitabine has been withdrawn, although zidovudine still has a role to play for some patients.

PROFESSOR TUDOR-WILLIAMS: Yeah, and that's very short-term treatment, for the infants.

MS SCOTT: Can I ask you in particular about lipoatrophy, subcutaneous fat loss, because that is a stigmatising side effect.

DR WILLIAMS: It is. That is still something a lot of people who -- who were treated with these first generation therapies still have a problem with, and I still see lots of patients who have had -- developed lipoatrophy and who continue to need to have dermatological fillers to help alleviate that. The reason why lipoatrophy occurred is because, like I said, normally these drugs had an effect on the mitochondrial cells. The mitochondria are the -- are the energy parts of the cell, and they would affect how these cells functioned and it is in fat cells -- it

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made them lose fat cells, and so they developed this lipoatrophy which was, as you rightly say, quite stigmatising in terms of appearances.

PROFESSOR COOKE: Again, we still have specialist services that are operating now providing what we call "New-Fill", to try to fill in that lipoatrophy for patients. It is still a very common issue and one that patients find very difficult I think.

MS EDWARDS: Is it worth just mentioning the actual -- what happens. This is a very -- what's the expression -- where sunken, sunken cheeks -- and it's actually the other drugs with the buffalo hump, isn't it? Yeah.

So -- and unfortunately, what that looked like was like having AIDS, and so for lots of people that was very difficult because they'd got through the point where they didn't look like the pictures of people with having -- who had AIDS, and then when you go on these drugs you did, despite the fact you were actually maybe being treated and potentially getting a little bit better. So -- thus the stigma.

MS SCOTT: Then came dual therapy. Again, can you give us an outline of how that came about.

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DR WILLIAMS: Well, again, the virology of HIV, how it developed -- along the same lines we don't know everything about the virus, but it became apparent that if -- virus isolated from people being on zidovudine for six months was more resistant to zidovudine than virus taken at baseline. So it became apparent that the virus was changing. It was mutating to become resistant. And we know now that's because of, as I said earlier, the virus replicates at a high level, it does not proofread itself, it introduced errors, and so it can -- and so any mutations that are introduced which are -- are -- mean that it is less susceptible to that drug will emerge. So dual therapy came along when we had access to didanosine and zalcitabine, and people then looked to see whether maybe taking two drugs as combination therapy, and there was a large trial which showed that there was, again, impact in terms of 30 to 40 per cent improvement in mortality associated with taking dual therapy, but people still -- as I said in the report, people still continued to die. It wasn't -- you know, it wasn't a -- it was an improvement but there

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were -- people still progressed and people still failed therapy. We know now it's because the -- yes, it improved -- it stopped -- at the end, the viral load went down further but it wasn't sufficient to stop the virus from mutating, developing resistance, and then for the viral load coming back up again, and then ongoing damage to the immune system recurring and people fell ill.

So these effects were time-limited in terms of it's rather like you say cancer chemotherapy might work out then you have a relapse. It's the same sort of thing.

MS SCOTT: In terms of the burden of the medication, once patients are taking dual therapy can you speak to that.

DR WILLIAMS: Zidovudine used to be taken every four hours as Jane said that was the first sort of dosing schedule. But now for -- largely these were taken twice a day but some of the earlier formulations I sort of said before were very difficult. DDI in particular was very difficult drug to take because of its formulation. It improved over time but when the other drugs came along, then the pill burden increased. This is

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on a background of people who also had to take drugs to prevent them from getting the opportunistic infections that they had already experienced, so they were often on multiple, you know, doses of different drugs that made it impacted on their quality of life.

MS SCOTT: They are taking two toxic drugs now with side effects. Does that double the chances of having side effects?

DR WILLIAMS: I think it is important to understand these drugs were made available based on a randomised clinical trial that showed clinical outcome was better. So I think it's important to say that. Yes, they had side effects that we were no longer -- you know in today's regimens we would no longer tolerate but at the time large randomised control trials showed that taking two drugs was better than one in terms of improved mortality and people wanted to -- these things are taken one step at a time and you need evidence from randomised control trials to be able to say, well, that is a better standard of care. This is how you then move on.

MS SCOTT: In terms of the patient experience of taking those two drugs, was two worse than one

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commonly?

DR WILLIAMS: They clearly may have side effects one from the other, absolutely right. So as Graham has indicated some would have no side effects but side effects were very common. So diarrhoea from DDI, nausea and vomiting from zidovudine. So definitely it impacted on them, definitely.

MS SCOTT: Then we move on to triple therapy. Can you tell us about that.

DR WILLIAMS: Triple therapy came along when other classes of anti-retroviral drugs became available. So nevirapine was the first non-nucleoside reverse transcriptase inhibitor so it basically impacted on reverse transcriptase and then the integrase inhibitors -- sorry, not the integrase the protease inhibitors, particularly adenovir and adenovir came along in '96/97. These were drugs that acted in a different way to the NRTIs and trials of three drugs versus two drugs again showed an incremental improvement in terms of clinical benefit, and so trials of adenovir plus two nucleoside analogues were shown to be better than just two nucleoside analogues on their own.

At that point in time also trials had

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a clinical end point. They are looking to determining mortality rates and on progression to AIDS but then as we got to -- as the virology improved and we were able to measure the virus directly with new technologies, looking at virus detection assays, we could then monitor the effects of these drugs and the amount of virus in blood and it became -- from those large clinical end point studies it became apparent that if you are able to press the virus and keep it down and keep it suppressed then that resulted in an improvement in the immune system and so the changes in the surrogate markers, the CD4 count in the viral load captured the clinical benefits.

So it's rather like, for example, if you are treating high blood pressure, the outcome of high blood pressure is stroke but to do a clinical trial you do a clinical trial to look at its effect on blood pressure. So it wasn't until 1998, until the 1990s, that we moved from doing large clinical end point studies to doing trials which looked out viral load as an end point and, at that point in time, with triple combination therapy, I remember going to the

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Vancouver conference in 1996 and it was a fantastic experience and to be able to see these improvements with the triple combination therapy. It made a huge impact in being able to suppress the virus and the virus did not emerge with resistance. It maintained viral suppression.

MS SCOTT: In terms again of the patient experience of taking these medications, if we go back to the table that we were just looking at, there are an enormous amount of medications on this table and I don't want to go through all of them but could you just pick out for us where some particular medications or where a medication came on the market that seemed to be better tolerated by patients than the previous ones.

DR WILLIAMS: I suppose that didn't really come until the mid-2000s. Adenovir was a protease inhibitor but it was very difficult to take you had to take it three times a day, you had to have a high fluid intake. There were dietary restrictions and a high incidence of renal stones with it.

Ritonavir was originally a drug that was used for treatment of HIV infection but it was

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a really difficult drug to take in terms of its now only used as a booster for that.

Nevirapine was associated with quite severe rashes and people sometimes were admitted to hospital because of a severe rash associated with Nevirapine, although it is still a drug that we use quite a lot in people who can tolerate it.

As we move sort of through, so between 1998 through to the mid-2000s, other newer drugs emerged and new nucleoside analogues emerged in Lamivudine and in terms of tenofovir which didn't have this sort of side effect profile of the D drugs that I mentioned before and newer protease inhibitors became available such as darunavir and atazanavir which were better tolerated.

Protease inhibitors generally, particularly drugs like Kaletra contain lopinavir and ritonavir had really -- people had huge problems with gastrointestinal side effects like diarrhoea, a chronic problem and drugs like saquinavir also high dose burden, but also a lot of problems with diarrhea. Lopinavir, another one, these are early generation protease

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inhibitors. They advanced our knowledge. They helped us move forward, but they were by far ideal in terms of their pill burden, in terms of their side effect profile.

So it helped people but they had to deal with -- a lot of people had to deal with side effects. It wasn't really until I would say the mid-2000s and a bit later when the integrase inhibitors became available that we truly got drugs that were much better tolerated.

PROFESSOR ANDERSON: Just to add to what did Ian said, particularly about the early protease inhibitors, it was very hard to get a high enough level in the blood to get a therapeutic level, so you either had to take a lot of pills a lot of times a day or you had to take something which would help you boost it, which was where ritonavir came in. I have a very strong memory days of saquinavir when grapefruit juice was found to be something that could boost so people would have -- I can't remember -- handfuls of pills three times a day out and be advised to have grapefruit juice all in order to keep the -- just to get the drug level into the therapeutic range. So there was quite a lot

of -- and even if it wasn't necessarily causing a side effect it was certainly causing a lifestyle effect and then gastrointestinal symptoms which we are talking about as well.

There were difficulties in actually managing, in the early days of DDI you described those chalky pills. Before that it came as a sort of sachet of powder and you dispensed sort of a great shoe box of stuff and then we tried to make it flavoursome. Do you remember there was cherry flavour you could add and they were revolting. But again, as Ian has explained, they were making some sort of difference and so people put up with -- and we put up with prescribing things that were really difficult to take, not just making you feel unwell as well.

DR WILLIAMS: I still have patients I look after who accessed triple therapy for the first time in 1997 and it saved their lives. There's no doubt about that. Let's be very clear about that, the advent of triple therapy, high anti-retroviral therapy despite the problems of pill burden and side effects made a huge difference to some people.

PROFESSOR ANDERSON: Yes, absolutely echo that and I think we learnt -- we were seeing, after that, the Vancouver conference and the introduction of protease inhibitors, a really dramatic shift and actually the cost in lifestyle and all the other things, there was a benefit, a really clear benefit.

PROFESSOR TUDOR-WILLIAMS: I'd just like to say one thing. If you scroll right back to the top, there's a little line there that says for the interests of space we haven't included enfuvirtide but actually it's worth remembering that back in the '90s there was that interlude when we really had run out of new agents and T20 or enfuvirtide, which is right at the top of the table and not in the table, there, that line there, enfuvirtide, my memory was this was a twice daily injection that was subcutaneous and very difficult to reconstitute and actually caused a lot of injection sites reactions. But we were using it and our patients were -- I mean, again it bought time. It actually did tide people over long enough to survive to take advantage of triple combination therapy. But it was a really difficult drug to tolerate.

MS EDWARDS: Can I just make a couple of things and maybe again Gareth will pick up on this. It was a bit of a different game when you were talking about children and many of these drugs were not available for children, although some were, and you can expand on this. But I think from the nursing point of view, how do you get these young children to take these drugs? We've already described how hideous they were to take as an adult when you can rationalise what you're doing. But to try and give a child something so revolting was very, very challenging.

I think the second thing to say is the confidentiality issue that is associated with drugs because people had fridges full of drugs. They had bags full of drugs. I still know people today who make sure they take their drugs before they go to work and they are on one or two tablets a day. People were taking about 28 drugs. It was enormous amount of drugs, including some of the prophylaxis for opportunistic infections which reduced. But maybe you want to expand on the children because it was a different scenario for the families who had small children.

PROFESSOR TUDOR-WILLIAMS: Yes, okay. I don't want to spend too long but it was a challenge. The pharmaceutical industry, in fairness, was trying to work very hard with us to produce formulations that children could take but they were often -- I mean, ritonavir as a suspension is utterly repulsive and I wouldn't allow any doctor in our team, any new doctor joining, junior doctor, to prescribe ritonavir if they hadn't tasted it first so that they knew what they were actually having to -- what we were asking parents to do with their children.

We ended up quite often inserting gastrostomy tubes, a tube that will sit in the stomach wall, through which you can give the medicines simply because you can then avoid all the taste but pathways that were so difficult for parents to manage. It was a challenge.

MS SCOTT: I think you say in the report, Professor Tudor-Williams, that the drugs that did come on for children, the trials that did take place for children, were far letter than for adults.

PROFESSOR TUDOR-WILLIAMS: We tended to lag behind. We tended to have less choices and therefore

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children were kept on their first line therapy for longer and these were not easy therapies, so we ended up with, in those early days, unfortunately selecting out highly resistant virus in the population of the early-treated young people.

MS EDWARDS: Just to add one quick thing, which is of course some of these side effects also had issues around bleeding so if you had haemophilia you weren't able to take some of these drugs because of the problems with bleeding. I think we've written that somewhere.

MS SCOTT: Can you then take us up to the present day in terms of the history of the medications.

DR WILLIAMS: Yes, triple therapy definitely made a huge impact and certainly from '97/98 the incidence of new opportunistic infections -- this is when AIDS started to fall. We saw dramatic impact on both that and mortality. But the drugs were not ideal, so during the 2000s the integrase inhibitors became available, raltegravir in 2007 and the other integrase inhibitors later on and safer drugs in terms of nucleoside analogues like tenofovir also became available.

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The pill burden started to fall and people started to be able to take regimens that were once a day and now regimens that are in a single pill. They became more tolerable.

A pivotal study was the smart study done in the mid-2000s which looked -- because we -- to sort of consider what the thinking was at that time there was a sense that some of these drugs had sufficient high adverse events that maybe taking them periodically would be better than taking them all the time and, therefore, there was a trial that was done, randomised people to take medications periodically depending on their level of CD4 count in their blood versus taking therapy all the time. But that was -- the result of that trial was pivotal because it showed the control of virus all the time was far better. It had a far better improvement in clinical outcome.

So that changed the way we looked at things and then as medications become more tolerable, not to say they didn't have side effects but they became more tolerable in terms of people being able to take them better, then it became clear that we needed to start therapy

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in everybody.

It wasn't until 2015 where the outcome of a trial looking at early versus deferred anti-retroviral therapy where we showed that actually even if you take therapy as soon as you are diagnosed with a high CD4 count you have clinical benefit in terms of risk of progression to severe disease. It went down -- it sort of halved but it was only in terms of 4 per cent down to 1.6 per cent but told us that treatment at any level of CD4 count was important.

From 2015 guidelines changed which then indicated that people should be offered therapy at the point of diagnosis and Public Health England now monitor the outcome of therapy and we know that from recent data that there are those patients who are diagnosed and attending clinical care, 97 per cent of them on therapy, and of those who are on therapy 97 per cent have undetectable viral loads in terms of viral suppression.

Having said all that, that is a biological outcome in terms of viral suppression and that doesn't then -- one needs then to acknowledge what are the quality of life issues around

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taking therapy all the time and the other things that we talked about co-morbidities and everything else and mental health disease.

MS SCOTT: Just sticking then on the burden and the side effects of the modern treatment where are we in relation to that? How is that experienced?

DR WILLIAMS: Certainly someone starting anti-retroviral therapy today will have a much different experience than someone starting therapy 20 years ago. There's no doubt about that. Most people starting therapy for the first time today will take a regimen that mainly contained one or two pills and there will be drugs that are better tolerated. Their discontinuation rate due to side effects will be only a few per cent at one year and they will tend to continue to live normal lives and go to work. Yes, people experience side effects, as people experience side effects from any medication prescribed for any condition, but generally it is much better, right.

Having said that, those people who have been treated before they will often be on much more complex regimens because of issues around

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resistance. They may have developed resistance to the previous drugs and therefore their regimens may be more complex. They may be twice a day, maybe more medications within them and they may therefore have more sides effects associated with that. So it's very different from someone starting therapy for the first time, diagnosed today, compared to someone who has been on therapy to 20 years where they have the burden of problems from over 20 years and what may be needed from therapy in them compared to someone who is naive to therapy.

MS SCOTT: You have said that the 97 per cent of those who take anti-retroviral therapy have reduced their viral load to undetectable amounts. Can you explain what that actually means.

DR WILLIAMS: Again, that's a very biological outcome to a certain extent and I think it's important not to -- one needs to emphasise the other impacts of taking therapy for a long time are, and we've alluded to that earlier.

What that means is that if you suppress the virus, the virus is therefore unable to change and mutate, right, and therefore you

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don't develop resistance. Resistance is not developed and therefore people -- there's no -- there's absolutely no reason that as long as you continue to suppress the virus through anti-retroviral therapy that people will not fail therapy, and the main reason why that will occur, as long as people are able to adhere to therapy, so one of the things that is very important about treatment is that people need to take -- need to adhere to therapy at a high level so more than 90 per cent of medications, so that in itself is also something, you know, important to emphasise and to do.

But what the viral suppression allows, it allows the immune system to improve, right. I alluded to earlier rather like being on a treadmill. If you can come off the treadmill you recover and that's exactly what happens. It allows the immune system to recover, it allows it to rebuild itself and it allows the immune system to do what it should do, which is to prevent other infections occurring.

Clearly starting therapy at a higher level, at a higher CD4 count, is better than starting therapy at a lower CD4 count because

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you are having to rebuild the immune system from a very low level, not that it can't be done but it's associated with more morbidity.

MS SCOTT: Once a viral load is undetectable, is it right that it's been known for some time that that means that it's not untransmittable?

DR WILLIAMS: Yes. I mean, the viral undetectable is basically based on an assay we use to monitor viral load in blood. It's not to say the virus has gone away. The virus is still there in cells that are quiescent and latent and if you were to stop therapy, the viral load comes back up again.

MS SCOTT: So it has not been cured.

DR WILLIAMS: Not been cured. It's about maintaining viral suppression through drugs that inhibit viral replication. It's not about cure or eradication. That is very much the goal that scientists are trying to look at but at the moment in time therapy is lifelong and people have to take lifelong therapy every day. So that's again that has an impact in terms of how people see also themselves as a chronic condition.

PROFESSOR ANDERSON: I think it is also important to

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just reinforce Ian's point about undetectable. So the terminology has come from the laboratory assays and the level that we call undetectable has changed as the assays have got more sophisticated, so it is about looking in the blood to see how much viral replication is going on. In the early tests, you could find 400 copies per ml and that would be the level of detection. Then it went down to 100 with a more sensitive assay, then it went down to 50, then it went down to 20, so it's about -- it's referring to what the laboratory tests can do and the sensitivity of it. So it is undetectable on the test and, again, it's really important it's not gone away, it's just that the test has got to the limit of its sensitivity.

DR WILLIAMS: Also you alluded to the question about being untransmittable. Certainly, if you reduce the virus in blood, you reduce the genital fluids, therefore, we now know again from randomised control trials that if you go on to therapy you reduce the risk of transmission to an uninfected partner by 95/96 per cent.

MS SCOTT: Through having sexual relations?

DR WILLIAMS: That's right.

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PROFESSOR ANDERSON: Again, from vertical transmission, the greatest risk factor for vertical transmission is how viral load in the mother and a woman who has an undetectable viral load, the risk of transmission is -- well, Gareth?
PROFESSOR TUDOR-WILLIAMS: Less than 1 in 1,000.
MS SCOTT: How about transmission via blood?
MS EDWARDS: Wherever, it's all about viral load.
DR WILLIAMS: I would have to say there isn't the same level of evidence, right, in terms of, for example, in injecting drug users and clearly blood products are now screened for that, so there isn't that evidence. So the evidence comes from sexual transmission because that's where ongoing transmission occurred.
PROFESSOR COOKE: It's difficult to really underestimate the transformative impact triple therapy has had, not just to individuals but for the management of the whole disease. It transformed what was essentially a disease of progressed immunosuppression which was managed in hospitals, in my own setting, where I imagine, James, at the time, there may have been 40 or 50 patients in that hospital and we

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now have maybe three or four.

What has happened is we have moved HIV to a much more of a chronic disease, like we might manage diabetes or hypertension, which is in outpatient clinics and we now have maybe 100,000 patients in the country on this treatment, and it was really in the middle of the 1990s that that transformative change came about.

PROFESSOR ANDERSON: Absolutely. I think the other thing which Sian has alluded to is the need to continue therapy. Something I hear from patients is the reminder that every time you take a pill you're still living with HIV and sometimes that can be a barrier to adherence because it's a constant reminder. There are some drugs at the moment only in clinical trials which are looking at either longer term injectables or depos which may again change the field, but for the moment somebody will need to take tablets every day.
MS SCOTT: You told us that the anti-retroviral therapy, for 97 per cent of those that take it, is highly effective. Is it more effective for somebody that is newly infected and goes on to those therapies, those modern therapies, rather

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than someone that has had HIV and been living with it for a long time?
DR WILLIAMS: The thing that determines response is the ability to take the medication. It depends on your previous exposure and development of resistance and on other co-morbidities that might impact on side effects. So, yes, someone who is diagnosed now at an earlier age is likely to have a much better experience than someone diagnosed -- well, they will have a much better experience than someone diagnosed 20 years ago.
PROFESSOR COOKE: We have now really touched on life expectancy, so we would expect that if someone was diagnosed now in a timely way, able to take that treatment every day, that their life expectancy would, as far as we can tell, be the same as if they didn't have HIV at this point and that was obviously not the case for a very long period of time.
MS SCOTT: Just picking up on that point and developing it further, for someone who has been living with HIV for a long time but is on these modern drugs now and who has undetectable viral load, what is their life expectancy?
DR WILLIAMS: Can I just -- I'll answer that

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question but quickly come back to the fact that in terms -- I don't want -- get the Inquiry to understand that although these modern drugs are much better tolerated, they are not without their issues for individual patients, so sleeping difficulties can still occur, anxiety for some patients, gastrointestinal symptoms, loss of bone density, so there are things that need to be monitored for even with these modern drugs, but they are, compared to the older drugs, are much better. So I would not want the Inquiry to think that they are absolutely perfect because they are not. They are much better than they used to be and people tolerate them much better but there are ongoing issues where we would like to improve on them.
PROFESSOR COOKE: One of the more common things we still deal with is neural psychiatric effects, even from drugs today, often relatively mild and not as common as they used to be but nonetheless there and even with the new options we have we still sometimes have to rely on drugs which cause that and that obviously adds to issues that might exist before those drugs are started.
MS EDWARDS: Can I add one thing onto this as well

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and that's I don't think we can underestimate adherence as an important component to this drug therapy. When you start newly on a drug and the doctor says you need to take this drug every day at the same time for the rest of your life, it is somewhat easier when you have been spending 20 years plus taking all sorts of drugs that may not have worked, you are very sick, you have been very sick, and we were talking earlier on about psychological impacts and that we know that the psychological impact of depression and anxiety has a very negative effect on adherence.

The second thing is about relationship with the healthcare service. I think that your relationship with your doctor, your relationship with your nurse, has a very strong correlation with how able you are, whether that is mentally or physically, to take these drugs and keep taking them at the same time every single day. So I think that history that you are talking about of people being unwell for a long time has a bigger impact on that aspect.

PROFESSOR ANDERSON: I think there's another aspect which I think you might come to but the increasing understanding of the importance of

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peer support in things like adherence and so within clinical settings making sure that there are people with the experience of living with HIV and taking medication who can support people on that part of their treatment, because actually sometimes having experiential expertise is incredibly helpful in helping with that.

MS SCOTT: I did ask a question about life expectancy but I can come back to that.

PROFESSOR TUDOR-WILLIAMS: Just on that point, because you asked the question about if you had been living with this for 20 years how could you -- what's it like taking today's drugs. From my experience, every time we look at -- we are constantly trying to find the best possible tolerated options for the young people as they are growing up and as we have more things to offer, but every time we look at that decision-making we go back and look at the archived resistance.

Ian mentioned this, the virus is very capable of lying dormant, latent inside cells for a very long time and the worry is that when you have been exposed to mono-therapy or dual therapy and you have archived those viruses with

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that resistance we take that into account when we think about the options today. I am sure it is true in adult practice, isn't it?

PROFESSOR ANDERSON: Yes.

MS SCOTT: What are the long-term effects of taking anti-retroviral therapy then, even the well tolerated drugs for people that are going to be taking it for a long time, for the rest of their lives?

DR WILLIAMS: I think the answer to that is we don't know, to be honest. Clearly we have experience from some of the older drugs in that people -- we have mentioned peripheral neuropathy. The symptoms of peripheral neuropathy can be long-standing and be a problem for many, many years, even after you have discontinued the drug that was causing the problem. Many of the earlier drugs like didanosine or stavudine have had long-term impacts on the liver and pancreas and people developing liver disease and pancreatic disease 10 or 15 years later. So there are those.

If you asked me what are the long-term impacts of the current modern drugs, we haven't as yet seen any signals to be concerned but like

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any long-term medication we need to continue to be robust in being able to identify that. There are, for example, tenofovir, there are two forms of tenofovir: one is tenof DF and one is tenof AF. Tenof DF was the first version. That can be associated with chronic kidney disease but it can be also associated with bone loss, but that's largely been replaced by a newer version of tenofovir.

Again, experience will tell us that there will be something down the line that may well -- which has not been identified in clinical trials. Often you identify in clinical trials what are the most common side effects but when you put the drug into a larger patient population than a clinic population then you experience problems associated with that drug in a more diverse patient population.

PROFESSOR COOKE: It's probably fair to say that we see these cycles of excitement and then tempering of that excitement over the years where we are dealing with patients with drugs where we know that they are not perfect, something new comes along, new and shiny, and everyone is excited about it and we tend to use

more of it, and then gradually often we have found there are side effects and have had to rein back. Still there will be some patients who benefit but we learned a bit more about it, even with the newest drugs we are still going through that cycle I think.

PROFESSOR ANDERSON: There's also an issue, I think Ian has alluded to it, the diversity, so as people who are living with HIV get older, not only are they taking drugs for a long time but they are physiologically changing, the human being is changing as well, so we don't necessarily know about how that's going to play out and there is far less data at the moment on women. They tend to be less well respected in clinical trials and older people are under-represented in clinical trials as well, so those are areas which we still have to find out about.

MS SCOTT: That was a question in fact that somebody specifically asked me to ask the Panel, which is what impact is the ageing process going to have on the effectiveness of these medications?

DR WILLIAMS: I don't think it's an impact on the effectiveness because I think as long as people

take the medication then the viral replication cycle will be prevented. But clearly as people get older the dose of the drugs might need to be adjusted.

We know little about that because of the way the drugs are handled by an individual as they get older, but I think there is an important issue about whether HIV has an impact on ageing in terms of the interface with someone getting older and the interface of disease associated with ageing and HIV, and whether there is -- HIV is associated with either accelerated ageing or attenuated ageing. It's generally thought to be associated with attenuation, that diseases of ageing tend to be more common in people with HIV rather than premature.

MS SCOTT: Is there anything anyone else wanted to say about medication before I pick up on the life expectancy question?

So we started to digress into life expectancy and I think what you said was for somebody who's newly infected and goes on to these modern drugs, life expectancy is pretty much as it is for somebody that doesn't have

HIV.

The next obvious question is, well, what's the impact on life expectancy compared to somebody that doesn't have HIV?

SIR BRIAN LANGSTAFF: May I just ask a question about that. It really arises out of what you were saying about the long-term effects of having drugs. It must be the case that no-one in the UK has suffered from AIDS for longer than 40 years, so so far as those with haemophilia are concerned the cohort may be largely younger than older. We just -- how do we know what the life expectancy is going to be?

[Applause]

PROFESSOR ANDERSON: I don't think we do.

DR WILLIAMS: We don't know the answer, Sir Brian. I think that's a very important point and I think all we can do is estimate through epidemiological models. So people more with experience in epidemiology and life expectancy are the ones who have looked at this, but what they do is they look at the incidence of different diseases associated in someone who is aged 60 or 70 and they extrapolate from there in terms of what the deemed life expectancy is.

But no, you are absolutely right, I don't know what's around the corner in terms of this. There could be something that could develop, that would be, you know, that is unexpected but experience to date suggests that once you -- when people have been on therapy for a long time and they have recovered their immune system, then generally they live -- their incidence of disease associated with severe immunosuppression is no longer there but what there is a concern about is, which I alluded to earlier in the previous session, was the fact there are issues around diseases of ageing and cancers. That's what I am seeing now in my cohort, is that --

SIR BRIAN LANGSTAFF: Presumably the effects of mental problems.

DR WILLIAMS: Absolutely, yes. Absolutely right. So living longer is fine but living well and longer is really important and that's where we at this moment in time can't guarantee that.

MS SCOTT: Turning then to those that have been living with HIV for many years, what do we know about life expectancy for those patients?

DR WILLIAMS: I think it's a really -- I think it's a question that I can't answer to a certain

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extent because I don't think we have, you know, as I said before, there are epidemiological models which can model this but most people, the way they publish this data, is looking at someone diagnosed now, right.

Someone living, you know, who has been living with HIV for 20/25 years has had a damaged immune system for much longer time than someone who is diagnosed now. Having a damaged immune system for a long period of time has its long-term sequelae, particularly in terms of cancers.

As I said, frailty is a problem in people getting older with HIV because it's not just about living longer, it's about the quality of life, and frailty in someone with HIV living longer is much higher so they tend to have much more conditions of ageing, the prevalence of those conditions is higher, right. Therefore, diabetes, blood pressure problems, cardiovascular disease, renal disease, they tend to have more complex problems. So, yes, life expectancy has improved a great deal but where we are now is trying to improve and reduce these other conditions that impact on frailty and

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quality of life.

MS SCOTT: Professor Tudor-Williams, can I ask you from your perspective the same question. In your report you suggest that outcomes are better for those that were infected between the ages of 5 to 15, as I understand it, in terms of life expectancy. Is there any other information that you are able to share with us about that?

PROFESSOR TUDOR-WILLIAMS: I mean, there is limited data specifically from haemophiliac cohorts looking at that kind of actuarial survival that would suggest that those that were infected at a younger age have done better than those infected who were older. I think that just simply reflects the older ones already had co-morbidities that were prejudicial, that gave a survival advantage if you are infected younger.

I think -- I tried to put a little bit of data into the report relating to our cohort of young people who have been living with the virus that was perinatally acquired, so they reached their 20s having already lived with the virus for 20 years. It's clear that there are increased morbidities and mortality rate that is

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related to both an increased risk of cancer, some increased risk of mental health issues. Our own cohort data shows that there's probably a 13 per cent higher incidence in our young people up to the age of 24 compared to the non-HIV infected same population and also a 20 per cent likelihood of mental health issues with three of our cohort who have attempted suicide.

I think, therefore, it's incredibly difficult, as I said, that the long-term outcomes for the young people who are infected surviving into adulthood are really difficult to model at the moment and I think we would be unwise to be drawn into guesswork about what the future holds because whilst there may be some unexpected and adverse problems lying ahead, equally there may be some amazing breakthroughs that everybody's going to be able to take advantage of.

I remain an eternal optimist from that point of view and I really hope that anything we say today will be trumped by advances in therapy tomorrow.

MS EDWARDS: Can I say that I don't think we can

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underestimate the mental health issues. We're not talking about -- we're talking about mental health issues about, certainly with people who have had haemophilia who were diagnosed very young, and all that whole issue of the problems with schooling, the problems with lack of interest or ability to have a future that they could hold on to, they have been told that they were going to die. They've watched their friends die. They have watched their brothers die, you know, and we've discussed all this on Tuesday but I think that it's a profound effect on the mental health.

So if you have been living not only with these physical illnesses that we have been talking about, these long-term treatments we have been talking about but also a sort of a loss and grief in your life that there's a lot to deal with that interrelate with one another.

MS SCOTT: Sir, I note the time. If this is a convenient time to break we will be collecting questions from any core participants to be put to the expert Panel in the last session.

SIR BRIAN LANGSTAFF: Thank you for that. I think it probably is convenient. Let us be back here

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then at 3.30.
(3.01 pm)
(A short break)
(3.30 pm)
SIR BRIAN LANGSTAFF: Before we turn to the next topic, could I just check something with you and see that I understand it correctly, and you can tell me where I've gone wrong.
Can we have a look, please, Henry, at what -- the picture on page 3 -- it's a couple of pages further on. That's the one.
This is described as HIV treatment explained. To understand what the explanation actually is, can I just see that my understanding is right.
The little dot at the top, the -- labelled "HIV", that's where one starts with -- that's the viral particle. The big circle in the middle is the cell, with the nucleus in the centre, and the net result of the viral particle entering the cell is to render the cell ineffective at doing its job in the immune system and you end up with -- well, here it shows five little particles coming out of the far end.

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I suspect that's representational but it means that one viral particle comes in, a number of -- more come out, it clones itself?
You are nodding. That's for the transcript.
PROFESSOR ANDERSON: Yes.
DR WILLIAMS: If I can say that the nucleus is rather like a computer, and so what the virus is doing is basically encoding itself into the computer.
SIR BRIAN LANGSTAFF: Can we just take it stage by stage.
First of all, it's got -- this viral particle has got to get into the cell, through the cell wall.
DR WILLIAMS: That's right.
SIR BRIAN LANGSTAFF: You mentioned earlier, though I don't think it's shown directly on this, the importance of the CCR5 co-receptor, which some cells don't have, most do, and it's by binding to those, is it, that the particle can get in, into the centre of the cell?
DR WILLIAMS: Yes, there's three stages to HIV entry. There's the -- the virus will bind directly to a CD4 molecule, through its gp120,

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then it will then bind to the co-receptor, which is either CCR5 but there are others, and then it will -- then there's a third stage, which is fusion with the cell membrane, which then allows the virus to inject the viral RNA into the cell cytoplasm.
SIR BRIAN LANGSTAFF: So here we are with the orange arrow showing the little particle coming through the cell wall, and then at stage 3 we have the HIV RNA. Now you have described how HIV consists of a strand of RNA, whereas what is in a cell, gives you the cellular message, is DNA.
DR WILLIAMS: That's right.
SIR BRIAN LANGSTAFF: Reverse transcription is creating DNA out of RNA, is it, rather than the other way round, which is transcription --
DR WILLIAMS: Yes.
SIR BRIAN LANGSTAFF: -- since reverse transcription?
PROFESSOR ANDERSON: Yes, exactly.
SIR BRIAN LANGSTAFF: So there we see the two separate strands of RNA combining to form a dual strand?
DR WILLIAMS: It's a single strand of RNA.
SIR BRIAN LANGSTAFF: Single strand? Right. So

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there are two single strands but it curls itself round to the double helix.
DR WILLIAMS: Absolutely, into a double strand of DNA.
SIR BRIAN LANGSTAFF: So you've got a bit of DNA but it's not a complete bit of DNA, not a complete --
DR WILLIAMS: It's the viral -- it's encode -- code -- it's all the viral genes, right, but it's in a DNA rather than RNA copy, and so it allows the DNA then to be encoded into the cell nucleus.
SIR BRIAN LANGSTAFF: And if it is encoded in that way then it can replicate?
DR WILLIAMS: Because when the cell is then activated, the cell reads its -- the DNA in its nucleus and will then produce new products as a result of reading its cell -- its cell DNA.
PROFESSOR COOKE: It's that integration that makes a cure so difficult that is different from other viruses, so that that DNA is then integrated into a -- the human DNA.
SIR BRIAN LANGSTAFF: Right. So the first stage is entry, the second stage is reverse transcription, and then once this bit of DNA has been produced, it has to be integrated into the

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centre of the cell. That's the integration that's stage 4, I think, as shown here.
PROFESSOR ANDERSON: That's right.
SIR BRIAN LANGSTAFF: Then, having got in, the new viral material is produced, and that's what you say -- you say -- or the diagram says here it's cut and assembled by protease, which is another protein, is it?
DR WILLIAMS: Yes, it's the -- the virus encodes with three enzymes. It has three enzyme products, which is reverse transcriptase, integrase and protease, and it needs all those three enzymes to be able to produce a new virus particle.
SIR BRIAN LANGSTAFF: And each of them at a different stage.
DR WILLIAMS: That's right.
SIR BRIAN LANGSTAFF: So there's the entry first of all, there's reverse transcriptase, the enzyme which allows for reverse transcription. Then you have integrase which allows it to integrate into the centre of the cell. Having got into the centre of the cell, it starts to reproduce, and that's when you need protease --
DR WILLIAMS: It will reproduce -- reproduce only if

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the cell is activated. So if the cell is not activated, the viral DNA -- pro-viral DNA will remain in the cell nucleus and the cell will become a resting T cell which might live for many tens of years. And that is the reservoir of HIV infection that is so difficult to eliminate.
SIR BRIAN LANGSTAFF: So the way in which -- or the bits which the treatments you have told us about target are, first of all, you have told us about nucleoside and non-nucleoside reverse transcriptase inhibitors, and what -- the way that the non -- sorry, the way the nucleoside work is -- is that by competing with the --
DR WILLIAMS: So it competes -- when you -- when you build a DNA you need to build it with building blocks, nucleic acids, okay? So the things like zidovudine are -- are analogues of nucleic acids, right, and so they compete with the active site of the enzyme to get -- to be put in -- into the expanding DNA chain. So that is part -- that's the sort of -- competitive sort of inhibition.
SIR BRIAN LANGSTAFF: So to use a homely analogy, it's a bit like elbowing the virus aside, trying

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to get -- trying to get into the queue.
DR WILLIAMS: That's right, yes, yes.
SIR BRIAN LANGSTAFF: Like a tube train, some people may get on and some people may not.
DR WILLIAMS: Yes.
SIR BRIAN LANGSTAFF: So then the integration, that's the integrase inhibitor, and -- oh, I haven't asked you about the non-nucleoside. Does that deal with the process of transcripting -- (overspeaking)
DR WILLIAMS: What the non-nucleoside does is that it binds something slightly separate to -- slightly distant to the active site of the enzyme, but in doing so it distorts the active site and therefore the substrate, which is the nucleic acid, can no longer be bound to it and, therefore, it stops the work of the -- of the enzyme.
PROFESSOR TUDOR-WILLIAMS: It sort of buckles the door of the tube train.
SIR BRIAN LANGSTAFF: That's what I thought, yes, thank you.
MS EDWARDS: It's like a zip, in fact, you know, the teeth of a zip. And you can -- if you -- one of the teeth of the zip doesn't work, then it won't

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go down. And the non-nucleosides, I -- this is how I explain it to nurses anyway -- and the non-nucleosides are like putting a bit of cotton or fluff in the actual zip at the top so you're not going to go anywhere at all. All those little teeth of the zip are like the nucleosides going down the zip.
SIR BRIAN LANGSTAFF: With the working of integrase, do you have an explanation for that?
DR WILLIAMS: Well, integrase will allow the DNA in a nucleus to be spliced and allow for the -- the pro-viral DNA to be inserted. So what it does is it stops that from happening and therefore the pro-viral DNA just loops itself round and is not encoded.
SIR BRIAN LANGSTAFF: So a sort of cut and paste.
DR WILLIAMS: That's right, yes.
SIR BRIAN LANGSTAFF: Then the --
DR WILLIAMS: Not pasted, just cut.
SIR BRIAN LANGSTAFF: Just pasting --
MS EDWARDS: No pasting.
SIR BRIAN LANGSTAFF: No, right. Sorry.
And then the protease, that's taking apart proteins and reassembling them in the --
DR WILLIAMS: Yes, so larger -- the -- when the cell

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is activated it will produce new viral RNA, and it will produce new messenger RNA, and the messenger RNA is responsible for producing large polyproteins, and those polyproteins need to be spliced in order to have a mature virus particle.

SIR BRIAN LANGSTAFF: When we're talking about triple therapy, it might be thought that what the -- the aim of the therapy would be to have something which stopped reverse transcription, something which stopped integration, and something which hindered reassembly by protease.

Is it like that or do we actually have two different drugs which have a go at reverse transcription?

DR WILLIAMS: All -- all you really need to be able to do is to stop the virus from mutating. Right? So it stops -- you can stop the virus replicating, right, but what you don't want to do is allow the virus to slip out and transform itself to something that will still replicate in the presence of drug. If you have -- it's rather like if you treat TB, TB, if you only give it one drug, it will get resistance very quickly. You need combination therapy to treat

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TB. So it's the same sort of thing.

Because the drugs are acting at different sites and there's more than -- there's three of them involved, then it's much more complex and much more difficult for the virus to escape that sort of hold.

SIR BRIAN LANGSTAFF: Essentially that's how triple therapy works, is it?

PROFESSOR COOKE: To answer your question there, then, it's unusual to have one of each.

PROFESSOR ANDERSON: Exactly, yes.

PROFESSOR COOKE: It does tend, partly for historical reasons, to be two drugs targeting the reverse transcriptase, combined with one other.

PROFESSOR ANDERSON: Exactly.

PROFESSOR COOKE: At least when you start.

PROFESSOR ANDERSON: So the "triple" means three different molecular drugs, not three different sites of action.

SIR BRIAN LANGSTAFF: But -- and one site of action will almost always be reverse transcriptase?

PROFESSOR ANDERSON: At the moment, yes.

SIR BRIAN LANGSTAFF: And it may be one of the other sites.

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PROFESSOR ANDERSON: Exactly.

SIR BRIAN LANGSTAFF: Did I understand the -- from your report that -- we have four stages. Entry is the first stage, which is not necessarily the same sort of enzyme process as the other three, but that there are now drugs which are being developed or have been developed to stop entry as well?

PROFESSOR ANDERSON: Yes.

PROFESSOR COOKE: Yes.

SIR BRIAN LANGSTAFF: Right.

PROFESSOR TUDOR-WILLIAMS: T20 was an example of that totally new class of drugs, which is why it was effective in the face of a lot of resistance to reverse transcription, for instance.

So once you got reverse transcriptase that was no longer inhibited by the existing drugs, T20 blocked that whole fusion process, and there are now new molecules in that class being developed.

SIR BRIAN LANGSTAFF: But there's no point in doing all four together? All four stages?

MS EDWARDS: We're getting down to two --

PROFESSOR COOKE: Generally where there have been trials done of comparing four versus three,

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generally there hasn't been any advantage to doing that.

MS EDWARDS: And in fact latest trials are actually going down to two drugs now.

SIR BRIAN LANGSTAFF: Ah, right.

PROFESSOR ANDERSON: And some of the other entry inhibitors block some of the co-receptors as well, so there are molecules that can block other bits of entry.

DR WILLIAMS: What is important is the drug has a high genetic barrier to resistance. So if the virus needs to do a lot more work to get resistance to that drug, then that drug is then generally more successful. But it only needs one nucleic acid chain to get resistance, then that means that's a low genetic barrier drug.

SIR BRIAN LANGSTAFF: Thank you very much indeed. I don't know if there are any questions which arise out of that for you, Ms Scott?

MS SCOTT: I don't think so, sir.

SIR BRIAN LANGSTAFF: That is all I am going to ask for the moment.

MS SCOTT: In your report you've got a section on the impact of HIV on those with blood and bleeding disorders. Professor Rockstroh is

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coming to give evidence tomorrow, and you have told me that he is the best person to direct those questions to; is that right?

DR WILLIAMS: Yes.

MS SCOTT: So then can I move on then to the parts of your report that deal with the information that should be given to patients. I am going to ask you a couple of questions about diagnosis and then pick the report up at page 61 about what should be given to patients on diagnosis.

The Inquiry has heard lots or evidence from different people infected by HIV that they were not told of their diagnoses at the time that the tests -- that it was discovered that they were HIV positive.

Can I ask you whether or not it's ever been acceptable to withhold an HIV diagnosis from an adult patient with capacity?

PROFESSOR ANDERSON: No.

DR WILLIAMS: No.

MS SCOTT: Has it ever been acceptable to withhold the diagnosis of HIV of a child from a parent with capacity?

PROFESSOR TUDOR-WILLIAMS: No.

MS SCOTT: Just sticking with then the diagnosis,

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Professor Tudor-Williams, you in your report -- you, and your -- in the section of the report I believe you authored -- about children and adolescents make some comments about how practice has changed in terms of informing young people of their diagnosis of HIV themselves. Can you just tell us about that.

PROFESSOR TUDOR-WILLIAMS: So back in the early days when we didn't have very great treatments to offer, there was a huge worry and -- I mean, obviously much of my experience was with young people who were infected as a result of vertical transmission rather than through blood products. Of the children in this country who were infected through blood products it was about 10 per cent of the overall two and a half thousand or so children who have lived with HIV. So there were many reasons -- we were very often -- it was a family condition, we were very often dealing with parents whose were themselves infected, who were dealing with their own feelings about that diagnosis, and who found it extraordinarily difficult to allow us to tell the young people growing up with HIV that that was their diagnosis. And the result was that we

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very often, not through our own desire but out of respect with dealing with the family's wishes, delayed telling the young people. And they would say, "Well, no, no, no, they are just about to go to secondary school, that's not a good time for them to know", and "No, no, no, they're just -- you know, they're not really into puberty yet so let's do it when they have gone through puberty." All sorts of reasoning would postpone us from letting the young person themselves know the name of the virus.

I think part of that was because of the whole tombstone campaign and the huge stigma that was associated with it. They didn't want their -- their children to be burdened with this knowledge. But what we learned over the years was that in fact if you discover that you are living with a sexually transmissible virus at the time that you go through puberty and at the time you start negotiating intimate relationships, that is a disaster. That is really difficult for young people to cope with. And it is much, much better if they assimilate that knowledge long before they are into any kind of those personal relationship issues.

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And over the years we've really come to the point where we are much more, I think, paternalistic in a way with the parents and say, "Actually, we really -- in this instance we really do know best, please trust us, it's going to be a great deal better if your young -- if the youngster -- you know, who's your responsibility, your child, knows about this at ten or eleven years of age", with the name of the virus when it's not really a big deal. You know, HIV, human immunodeficiency virus, it's just a name, and it doesn't carry an enormous amount of weight.

And then all of the education that goes on from that time forward prepares them to understand both themselves, where they stand in relation to other people, and we help -- I mean, what has made an enormous difference is this equation U equals U, undetectable equals untransmissible, so that they grow up -- and -- and we're already in that position to be able to say, "Look here on the computer is your viral load. It's undetectable. That's great. It means that you will not pass this on to anybody else, provided you can keep taking the

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medicine."

So it sets them up for a much, much better psychological experience going through adolescence.

MS SCOTT: You were talking about the name "HIV" not having any meaning to them because they are so young and they don't know about the stigma of the disease. Is that what you are describing?

PROFESSOR TUDOR-WILLIAMS: Well, it gets -- it gets over that hurdle of, "Oh no, we mustn't tell them the name of the virus." And actually, for younger kids, it's not a big deal. You know, it's just the name of a virus and -- and they don't go home and have sleepless nights about it, if you are 10 or 11. If you are 15 and you are hearing about it for the first time, that is really hard.

MS SCOTT: So that they learn about the virus and how to manage it before they understand the stigma and the psychosocial impacts and so on of it.

PROFESSOR TUDOR-WILLIAMS: Yes.

MS SCOTT: Can we then -- you deal with these issues in great detail in your report about the advice and the information that should be given to

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patients on first diagnosis and what should happen to them once they have been diagnosed in terms of signposting them on to secondary care, et cetera, referring them to secondary care, and you deal with it in great detail, and for those that have the report in front of them it starts at page 61. We can probably deal with this fairly quickly.

But can I ask you to explain what information should be shared with patients when they are being diagnosed, how that should be done and where patients should go after first diagnosis in terms of their HIV care.

PROFESSOR ANDERSON: So I think it depends. We've got two approaches we've put in the report. The first is -- David might want to speak to -- if somebody receives a new diagnosis outside a specialist setting and what happens in a specialist setting. Ultimately, the information is going to be the same; it's the pathway in, I guess.

However, I think what I would want to preface everything with is that information sharing and for people learning about what's happening is a process. There won't be a moment

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when you know everything or you know nothing, it will be a continuing ongoing discussion over -- after many different conversations. So this is a process for people to be able to have all the information that they need. But maybe if we were to say what would be happening to somebody who might have a test in a primary care setting where we would begin.

DR JOHNSTON: So testing in primary care is more common now than it used to be. There was almost a desire not to test at one stage. That has changed so now we will be testing in appropriate circumstances, and sometimes the result can be a surprise when it comes back or sometimes people are more prepared for that.

So what will simply happen is that you would try to see the patient, arrange an appointment for them to come in, and chat them through. And I think in primary care you would be giving them very basic information, showing them the support that any good primary care team should provide for any condition. So we're looking to provide care, understanding, respect, excellence, insofar as that is provided in primary care. But I think the key thing is

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communication, and assuring them that you are talking to their secondary care team, their specialist team, that they will be referred on, hopefully they will get a timely appointment to be seen. You give them advice. I think the key thing is also explaining that this is something that obviously will be a bit of a shock to them. If they do want to come back and have a chat with you, if they've any questions, often informing patients that it is entirely appropriate to write a little list -- often doctors are thought to hate lists, but in these circumstances, "Come back with a list, these are the questions that you may want answered." And then offering to see them after they have seen their specialist team. Because often they go and see the big doctor, the specialist doctor in the specialist centre, and that can seem quite daunting. And they will have questions because the experience can generate questions that can quite simply be answered in primary care.

And also, increasingly with specialist teams being at a distance, then there is much more that can be done in primary care in terms of follow-up blood tests and so on, so that

people don't have to make onerous journeys to have very basic tests done that can be done in their local setting. So it's facilitating the care and ensuring that patients know that they are on a sort of continuum of care and we're all on the one side trying to support them. I think that's what good care looks like now.

MS SCOTT: Out of that arises a couple of issues, one of which I know you are dealing with in the supplemental letter of instruction, but what you are describing requires those that are delivering care in primary setting to have some knowledge of HIV.

DR JOHNSTON: Yes.

MS SCOTT: And to be able to impart that to the patient, and you are going to be dealing with what training and so on medics working in those settings should be -- will have in the letter of -- in supplemental report.

PROFESSOR ANDERSON: Correct, yes.

DR JOHNSTON: So, again -- sorry, do you want me to comment on that?

MS SCOTT: Yes, please do.

DR JOHNSTON: Primary care, I mean, the number of patients with HIV in any individual GP's

practice will be relatively small. So, again, as a GP, you will go and perhaps just check what's available in your local service. You may even speak to the specialist team that you are going to be referring to, because I think satisfaction equals performance minus expectation, and if you say to somebody they are going to get an appointment in two days and they don't get it for three weeks, then they are feeling anxious. So you want to find out what you are offering them.

And also I think we would refer them to good sources of information because people as soon as they get this nowadays of course will go straight on to the internet, and the sources of information that come up aren't always just the most authoritative.

MS SCOTT: The other thing that comes out of there is the referral to secondary care. Professor Anderson, maybe you want to pick this up?

PROFESSOR ANDERSON: Yes, so there are national standards. Essentially in any service where HIV testing is being carried out, wherever it may be, there needs to be a clear mechanism and

a pathway for people who test positive to move into the appropriate care that they need after that. And that might be from primary care, it could be in community testing settings, it could be a variety of settings. But the national standard is that everybody with a new HIV diagnosis should see a specialist team within two weeks. If they have any symptoms whatsoever that should probably be within a couple of days, and if somebody is already in hospital and is having an HIV test as part of a work-up for a medical problem, the team with responsibility for HIV within that hospital should be seeing that patient within 24 hours. So those are the national standards that the British HIV association has set, and we would expect people then to be working within those confines.

Now, obviously, if somebody has an HIV test within, for example, a sexual health setting, they may actually be immediately able to meet somebody, and increasingly with point of care testing, you may find somebody who is having a test who is able to go straight from having a fingerprick test which is positive to meeting a specialist team potentially within hours.

So it depends a little bit on where testing is done but the bottom line standards are two weeks if you are well, two days if you are not, and 24 hours if you are sick.

MS SCOTT: And to a specialist team. So why is it so important?

PROFESSOR ANDERSON: So a specialist team -- and by that I am -- I am particularly talking about a specialist team because you won't necessarily meet a consultant immediately or a doctor but the team will have that special -- specialist knowledge.

So often somebody will -- the first person they will meet will be a specialist nurse who would be able to assess where people are at, because actually often some of the questions that people have require a bit more information than just a positive test. So to actually find out, start to take a full history, an examination, work out more information that's going to be able to inform the process going forward. So meeting a team of people who have got different skills, and -- and the majority of HIV care now is delivered through multidisciplinary teams. And we would also

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hope, and it's not universal, we would also hope that very early on -- and I am not going to say exactly how quickly -- somebody who has a new diagnosis of HIV would meet somebody else who's living with HIV and would be able to engage not only with professional expertise but with lived experience expertise as well.

MS SCOTT: So this was what you referred to earlier, the peer support, and the importance of that in getting people to understand the importance of taking medication and coming to terms with their diagnosis, et cetera.

PROFESSOR ANDERSON: Exactly, exactly. And a specialist team because -- and I think we've alluded to this before, there are -- we know now that the best outcomes, not only for the person but for public health as well, are to be starting therapy relatively quickly, and so having that specialist advice very early about what's available, what you might choose to take, what drugs would suit you best, when you want to start, do you want to start, how's it going to work, that's quite specialist information, but it needs to be given quite quickly. So it is really important that people have access to high

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quality, up-to-date, specialist knowledge about what is the best treatment for them which will allow them to have the best outcomes.

MS SCOTT: Then the wider issues that arise with an infection like HIV, transmission to partners, children, et cetera, the psychosocial impacts and so on, at what point do those get picked up? And again, what specialist skills are required in order to give patients care in respect of those issues?

PROFESSOR ANDERSON: So again, I think this -- it goes back to what I said at the very beginning: this is about a process, and there will be a multidisciplinary team with a variety of skills, and actually people probably need to meet a number of different professionals, either as a team together or one-to-one separately, but nonetheless it is really important that that expertise is available quickly but it may need multiple conversations before you cover absolutely everything.

So I think at the very beginning people usually want to know: okay, I have HIV, what's stage is it at? Am I ill? What's going to happen? What treatment would you -- shall

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I start? Those are the sort of -- you know, I guess, the immediate things, but actually the next question is: what sort of relationship are you in? Are you having sex with somebody? What are you going to do about -- what do you want to do about telling other people?

And where does that disclosure lie and how does that happen?

There are specialist health advisers within sexual health clinics, and the BHIVA standards recommend that everybody should have the expertise of somebody to talk about how you might want to have the conversations with significant others, including family members, and to start to think about children as well.

But those are big conversations. They don't happen, you know, in your first half-hour appointment. They are going to evolve over a period of time. Normally, and within our clinic and I think most clinics, somebody with a new diagnosis of HIV would be allocated about an hour of clinic time, and during that time would have probably a confirmatory test, they would have tests taken for CD4 count viral load, other baseline investigations. They're rarely

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-- they would rarely be done in primary care, although they might be. So not only would you be sharing information, you probably also would be gathering information at the same time, and then trying to piece the jigsaw together over subsequent visits.

MS SCOTT: And then once that initial prescription of medication has taken place, what does the care look like from then on in?

PROFESSOR ANDERSON: Well, I think, first of all, I wouldn't say "that initial prescription", I think you have to, first of all, think through -- I mean, you have heard from Ian, there are now multiple drugs on the market, multiple combinations, we have national guidelines, and there are alternative regimes that people may start. And also, you know, the idea that you are going to have a blood test one day and start treatment that's going to be for the rest of your life the next day, it's a big step. So often you may want to have some time to -- actually, the first -- it might even be the first few appointments -- thinking about what it means to start treatment, which is the best regime for you, which mixture is going to

work best, coming back with questions.

So, although increasingly people are being treated very quickly, and in some clinics people are being treated on the same day, I think normally people would want some space. So I don't think yet, and I am not going to say this is yet normal, that -- most people would probably leave their first visit with treatment information but not necessarily a prescription, and that prescription for some people may not be for some time yet.

Now, obviously, if somebody has got very advanced infection and they are very sick, or they are in a hospital bed, then things are going to move in a different way. I mean, I would also reflect back that if somebody has primary infection and a very high viral load, then that might be another indication to move very quickly with anti-retroviral therapy. But actually most people will want -- you have a lot to digest, as David was saying, and that requires processing before you go out with a prescription.

So the first few visits will be dependent on what the person needs, there will be perhaps

visits more close together, where blood test results taken on visit one would be discussed a week or so later, but it will not necessarily be all the same in one package for everybody. I don't know if that resonates with your practice --

DR WILLIAMS: No, I was going to say there were a couple of things where there -- if someone is diagnosed with an advanced disease with an opportunist infection, actually it may not be safe to start anti-retroviral therapy --

PROFESSOR ANDERSON: Actually, that's a good point.

DR WILLIAMS: -- straight away, because they -- starting anti-retroviral therapy improves the immune system and people can get what's known as immune reconstitution syndrome and people can be unwell. So, for example, in patients presenting with TB with advanced disease, we treat the TB first and then start the anti-retroviral therapy.

The other thing I think which drives, often, why people want to start therapy immediately is because they are concerned about onward transmission to others, and that is often a big drive in wanting to -- you know, they are

concerned about their own health but they're concerned about the health of their partners and such like.

MS SCOTT: Then once one's got over the initial stage, then what does -- what does the care look like? Is that delivered in specialist centres on an ongoing basis or do you discharge back to primary care once the viral load is --

PROFESSOR ANDERSON: So for most adult patients, let's assume -- excluding somebody who is very sick and in hospital with complications or has got an opportunistic infection, the initial period, probably a number of weeks -- and I'm not going to be more specific than that -- where the assessment, the baseline tests are done, a treatment plan is -- is considered, and things start to move forward. If somebody starts anti-retroviral therapy, you would want to see them again at least two -- four weeks later, so that you are able to see if the medication is suiting somebody, how it's going, checking in. Often there would be a phone line or a nurse or a pharmacist who you could talk to as you start treatment as you go through. And most people would have met a specialist pharmacist before

they start treatment to help with adherence.

So that period of starting treatment will require different amounts of support from different people. It would normally be happening in a specialist centre. And then once somebody is stable on their therapy, by which I mean they are happy with it, and it is working, viral load's going down, you would see them less often. But once the viral load is completely undetectable, you would be starting to think about even six-monthly appointments. But it will depend on each person individually what support they need in that first bit. But that will nearly always happen within specialist care with, if somebody has been tested in primary care, liaison with letters, assuming the patient gives consent for that to happen.

PROFESSOR TUDOR-WILLIAMS: Just one very quick point about the small kids. When we start anti-retroviral therapy on very young children, because their weight is changing and the drug dosage is dependent on the child's weight and their growth, we see them very frequently. We will be seeing them -- I mean, if we are starting under a year of age, we'll probably see

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them once a month, and then only as their growth stabilises out can we stretch those appointments out a bit more. But I mean most of my teenagers we're seeing maybe three times a year, in school holidays typically.

PROFESSOR ANDERSON: And I think there's also a sort of interesting phenomenon: if somebody has a new HIV diagnosis, a lot of other worries may come up. So something which before they had an HIV diagnosis they might have dismissed as a minor thing and not been worried about may become a much bigger worry: oh, is this a sign of something?

So having the availability of a phone line, somebody to be able to come in for an extra appointment if worries emerge is also very important. But that, again, will usually happen in a specialist setting.

MS SCOTT: The targets for referral on to specialist secondary care are short, ambitious ones. Are you aware of any resource -- of funding issues nationally which affect the provision of services or care or treatment for HIV?

PROFESSOR ANDERSON: Well, for the moment HIV treatment and care is free for everybody who is

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resident in the UK, and that's -- that's absolutely clear. So there should be no barrier for people to be able to access specialist care on a financial basis. And nobody should have to pay for that.

However, I do think it's important -- I would defer to David here -- how to access -- if your nearest specialist centre is an hour and a half on the bus, how do you want -- there are actual physical access barriers, which I think are important. And I think there's also the -- the disconnect, if you like, the way the funding flows, which is a bit more complicated, the money is there for specialist HIV treatment and care, but that's a different budget from some of the other care that people living with HIV might need. But in the short-term, there should not be a financial barrier for anybody having the HIV care that is appropriate for them.

DR WILLIAMS: Just quickly, it is a self-referral so you don't need actually a GP referral. So people can attend any centre they want. Which is unusual compared to other conditions.

PROFESSOR ANDERSON: That's really important. So the choice of where you might choose to go is

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also open, and the ability to go to either somewhere near you where you work or where you live is in your hands. You can choose.

MS EDWARDS: Can I just add one thing that -- that we wrote in the report as well, is that the centres and all the conversations that Jane just said, it's not just even the patient; you know, the families or significant person in somebody's life is very much part of this decision-making. And -- and we wrote this -- you know, if somebody wants to bring their partner, their child to this consultation, that would be encouraged as a holistic way of caring for somebody with HIV these days.

MS SCOTT: And one of the questions that's been left over to the supplemental report is: what is the optimum level -- what is the optimum model of care for somebody with HIV? And you are going to be addressing that in the supplemental letter.

PROFESSOR ANDERSON: We are going to be addressing that. I think in summary now though we can say that it needs to be person-centred, co-ordinated, joined up.

DR WILLIAMS: And integrated.

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PROFESSOR ANDERSON: And integrated with all the other things that are happening for somebody. And we will go into that in more detail.

MS SCOTT: That was the end of the questions that I had. I have a handful of questions from core participants.

Why do some people not contract HIV when exposed to the virus through blood products or blood transfusion? I think we addressed this briefly this morning.

PROFESSOR COOKE: I think we addressed this this morning to some extent. So it's a balance between the exposure risk, how much virus might be in whatever exposure there is, balanced with the susceptibility an individual might have, which might vary partly for genetic reasons and partly for other reasons. So those factors interplay.

MS SCOTT: Is it possible for somebody to clear HIV?

MS EDWARDS: Two cases?

DR WILLIAMS: There are people who are known as elite controllers who effectively -- through their immune systems, they are able to control, and if you're -- and they may well have an undetectable viral load but not on treatment,

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and they are at the one end -- another end of the spectrum. There have only been two cases of people who have eradicated HIV, usually through a bone -- a stem cell transplant -- stem cell transplantation for treatment of relapsed lymphoma. And this comes down to the -- using stem cells which don't express CCR5, which is what we alluded to earlier. They -- those stem cells mature into -- into the new immune system but they are -- cannot -- but they are no longer infected, cannot be infected by HIV because they don't express CCR5.

So there is a patient in Berlin, well publicised, called Mr Brown, and there's a case from The London Clinic, the clinic that I work at, which was publicised in February last year.

PROFESSOR COOKE: So we have a section in the report about cure, and I know it's a common question for patients in clinic continually. That's part of the answer to that, is that in theory it can be possible in a very small number of patients to have cure but it relies on quite extensive chemotherapy which can really only be justified when you have another reason to have it, in particular, cancer. So the cases Ian describes

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are both cases where patients needed chemotherapy and then had to have a bone marrow transplant. One of the research areas at the moment is to understand how that process could be done for more patients safely and at the moment we're not in a position to be doing that.

MS SCOTT: Just on the question of cure, yesterday when evidence was being given by the hepatitis expert panel, they were talking about curing hepatitis C. What is the difference between HIV and hepatitis C? Why is it HIV can't be cured?

PROFESSOR COOKE: It's partly as we were discussing earlier, this is a virus that integrates into the host DNA and can also pass between cells, even when therapy is effective. So trying to get rid of that virus completely from the body is very difficult, and it requires at the moment this quite radical approach to try and do that. Even in these two cases, and these are well publicised, they are undergoing close monitoring still because we don't really know the durability of these procedures when they happen, and Timothy Brown, I think, it has been over ten years now, but the most recent case is less than two years. So we're still learning what the

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durability of that could be in terms of whether the virus could come back. We think probably not but we don't know.

MS SCOTT: You mentioned elite controllers. Did I understand from your report that even elite controllers will, if they don't have treatment, they will lose control of the viral load ultimately?

PROFESSOR COOKE: Not necessarily, although a proportion will do. But there is a group of patients who appear to have an antibody response but don't have virus that re-emerges or at least hasn't yet.

PROFESSOR TUDOR-WILLIAMS: You just asked about hep C those in terms of what is the difference.

PROFESSOR COOKE: So hepatitis C doesn't have that process, as we discussed yesterday, where it would integrate into the host DNA, for example. So it's possible to eradicate the infection completely from the body more straightforwardly than it would be for HIV or hepatitis B, in fact.

MS SCOTT: Are the risks of infection in blood products and blood transfusions greater than exposure to the virus in other ways?

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DR WILLIAMS: The answer is yes.

PROFESSOR ANDERSON: We talked about that earlier.

DR WILLIAMS: It's a larger inoculum and directly given into blood. So if you are looking at sexual transmission, it's an inoculum within genital fluids and the amount of HIV is going to be smaller compared to a blood transfusion.

PROFESSOR COOKE: You will sometimes see that quoted as 100 per cent risk. I think, for reasons we've discussed, it's probably not that but some the reference texts that we have looked do actually use that sort of level of risk.

MS SCOTT: Does the fact of co-infection between HIV and HCV or HBV mean that the -- I think evidence was given or I asked a question about whether or not the fact of co-infection between hepatitis and HIV alters the natural course of HIV, to which the answer was no. The question that's asked is: does the fact of that co-infection, which means that the immune system is fighting the HIV, mean that in fact the patient is impacted indirectly? So the immune system is having to do more, it's on the treadmill, having to run twice as fast because it's got hepatitis and it's got HIV. So is it impacted in that

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way?
PROFESSOR COOKE: I mean, in a sense, it's difficult to be clear about that but certainly in terms of the sort of activity we talked about before, then the exhaustion and the weakening of the immune system has consequences for the control of other viruses as a result of HIV and that's both true for hepatitis B and for hepatitis C.
MS SCOTT: A similar-ish question: does the fact that someone is infected with HBV or HCV give rise to a greater statistical risk that they will also be infected with HIV?
PROFESSOR COOKE: In general, yes. It depends very much on the routes of exposure and the risks and the geographic location. But there are many shared routes of transmission. So overall there is an increased risk.
PROFESSOR ANDERSON: We would also say that hepatitis B and hepatitis C would be an indication for an HIV test. So it's really important.
PROFESSOR COOKE: Absolutely. Everybody with either of those the infections needs to be tested for HIV and potentially more than once if there's ongoing exposure risk.

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MS SCOTT: The virus HHV8 which causes Kaposi's sarcoma, is that transmitted via blood and blood products?
PROFESSOR COOKE: I'm not sure that's something we've looked at at this point.
DR WILLIAMS: It's largely transmitted sexually. That's the reason why it's much more common in men who have sex with men than in other affected patient populations. It is something we can certainly comment on.
PROFESSOR TUDOR-WILLIAMS: It can certainly be transmitted perinatally as well.
PROFESSOR ANDERSON: We can explore and put into our supplementary report any data that we find.
MS SCOTT: There are some questions that are of particular interest to women with bleeding disorders and they are this, that the Inquiry has heard evidence, that they experience more blood during menstruation so there's more blood on household items and more blood during intercourse. The questions that arise from that are: is there a higher risk of infection for those individuals through sex because there's more blood present?
PROFESSOR ANDERSON: If people are living with HIV

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with an undetectable viral load, it should make no difference. Graham, would you agree with that?
PROFESSOR COOKE: Yes. I think in the setting where people aren't on effective treatment it's harder to say. But generally where there is more blood during sexual intercourse we would imagine there would be more transmission. I don't think we have very good data on that.
PROFESSOR ANDERSON: I don't think there's very much data at all but, nonetheless, a woman who is on effective therapy should not be worrying about a sexual transmission during menstruation.
MS SCOTT: Equally, the concern about there's more blood around generally in their life, and so more blood on household items and so on, is are there an increased risk of infection to family from blood on household items.
DR WILLIAMS: No.
PROFESSOR ANDERSON: No, I don't know.
MS EDWARDS: Reiterate: it's the viral load. If the treatment which everybody should have access to now is effective and viral load is undetectable, whatever circumstances we're talking about will be the same answer.

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PROFESSOR ANDERSON: Yes.
MS SCOTT: These questions, as I understand it, are concerned with the historic position, so before effective treatment where the viral load was undetectable.
PROFESSOR COOKE: I think we haven't addressed issues in the report here related to specific haematological conditions and I think --
MS SCOTT: Perhaps those could be asked tomorrow of Professor Rockstroh.
MS EDWARDS: We know that the presence of blood that contains HIV can be transmitted to another person if it is blood-to-blood contact.
DR WILLIAMS: During sexual intercourse but, in terms of household items or looking after somebody with HIV, no. If people take precautions, you know, if they -- there have been reports of someone who is a carer who has acquired HIV through handling infected material from a patient, but that should not happen in terms of with universal precautions.
MS SCOTT: So one of the other questions that they ask is: how long does the virus live outside the body?
PROFESSOR ANDERSON: Very short.

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MS SCOTT: What does that mean? Seconds, minutes, hours?
MS EDWARDS: It doesn't -- effectively when you are talking about viral transmission, if you have blood on a kitchen table, even if it did live for two hours, you have still got to get it into a bloodstream. So what you have got to think is the issue about inoculum.
DR WILLIAMS: Often transmission occurs through cells. So cells are responsible for -- because the cells that are infected with HIV get transferred across and cells will die very quickly outside the body and blood.
MS EDWARDS: I think it's worth mentioning, though, that we may be talking in domestic situations where for something like children who had haemophilia who were bleeding, and I know that the bleeding is often joint bleeding but just something like profuse nosebleeds, which really are very, very profuse, the concern around a parent becoming infected from a child with HIV is a very real concern before we're talking about treatment when the idea of HIV in the blood is up there. That's a very real concern for people.

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PROFESSOR TUDOR-WILLIAMS: Can I add, it was a very real concern but actually the data as it emerged became immensely reassuring that there were, as far as I'm aware, absolutely zero transmissions to people caring for HIV infected youth. That's not true for hepatitis B.
MS EDWARDS: I was going to say hepatitis is different.
MS SCOTT: So another question they ask is would standard washing procedures destroy the virus, so we're talking about the blood on the table, wiping it away, that would get rid of the virus.
PROFESSOR ANDERSON: Yes.
MS EDWARDS: Absolutely.
MS SCOTT: Then questions about treatment. Were there any additional side effects of HIV treatment and I think here we're talking about the older treatments for those who were co-infected with hepatitis C.
PROFESSOR COOKE: There were and we also saw additive side effects from having combinations of treatments that would be potentially problematic and in the setting of inflammation in the liver, often one of the more common side effects we have not really touched on is

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inflammation in the liver as response to drugs, and in the setting of where there's already inflammation that can be exacerbated by the addition of HIV medication. So that's certainly something we recognise and in general patients who have co-infection with hepatitis tend to have more side effects from the same medication.
MS SCOTT: Is there a link between Truvada and kidney infection?
MS EDWARDS: Not kidney infection.
DR WILLIAMS: But one of the drugs in Truvada, that is a branded name, it contains emtricitabine and one of the early versions of tenofovir, tenofovir can have, as a side effect, can affect part of the functioning of the kidney and cause kidney -- renal toxicity. But it's something we monitor for.
MS EDWARDS: Yes, I was going to say people are monitored for all of these side effects very regularly.
PROFESSOR ANDERSON: But it's not related to kidney infection.
MS SCOTT: Another question about AZT treatment, the question is why would someone not have been given it, so were there any clinical

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contraindications for being prescribed AZT in the early days around 1987.
DR WILLIAMS: In 1987 it was given to people who were ill with AIDS and people who had symptomatic disease. If someone was HIV antibody positive but otherwise well there wasn't any evidence that giving AZT to those patients they would have benefit. So it's largely targeted for people who had life threatening illnesses and infections.
If, for example, someone had severe anaemia, then giving -- many people have thought about giving AZT because AZT can cause anaemia.
PROFESSOR ANDERSON: Actually there was quite a prominent and very disappointing trial called the concord trial because we had seen these improvements in life expectancy in people who were very sick, a trial was put into place to see if it would help people who were less sick and the results showed that it didn't make a difference and so that was where the decision-making came from about it being used in sicker patients at that stage.
MS EDWARDS: The side effects of AZT at the time, many people, it had a lot of bad press, and lots

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of people -- there was terminology around at the time, you know, it was the AZT that kills you, which obviously was not correct but people died despite being on treatment and so for some people they felt strongly they did not want to go on this drug and some medics would discourage it because of the fair comments around about the toxicities and the side effects.

MS SCOTT: That's another question. What is known about deaths being caused by that treatment?

DR WILLIAMS: I think -- in terms of what is known, as we were saying earlier, a lot of people felt that or it was put about that AZT was causing the deaths but it wasn't that, it was the AZT effect that was transient and, therefore, it only had short-term benefit and therefore people relapsed and went on to become ill as a result of their underlying HIV because the effective treatment of AZT was very short-term.

That's not to say, for example, someone having AZT and becoming anaemic did not, you know, have side effects from that. I mean, there have been deaths associated with anti-retroviral therapy, for example, some of the non-nucleosides can cause very severe rash,

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a Stevens-Johnson rash, which can result in a really -- rash and a severe hepatitis, and people have died as a result of that. I think there's --

PROFESSOR TUDOR-WILLIAMS: A sensitivity reaction, which is rather specific and genetically determined. But I think -- I mean, I remember very clearly coming back from the States in 1994 full of enthusiasm to use AZT to try and prevent or decrease the risk of mother to child transmission and finding my colleagues being vilified for using AZT because it was regarded at that moment in history as a poison, and that was an echo chamber that led to people demonstrating outside Great Ormond Street Hospital accusing people there who were very well meaning physicians, paediatricians, trying to do their very best to help, being castigated as murderers. I mean, it really was a very uncomfortable time.

PROFESSOR COOKE: I think it's worth emphasising, we have touched on this but it's worth emphasising, that because there was so much recognised toxicity with AZT and those early treatments they did tend to be left until they were really

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needed at a late stage, and so it was often quite a close association in time between starting them and death and I think it's quite understandable how people became concerned they were causing deaths but generally the evidence didn't support that directly.

MS SCOTT: Excuse me, I have one question on my phone so I am not just reading my text messages.

So this is a question in relation to the evidence that you gave about the immune system remaining hyper-activated and not returning to a resting state and we have a very, very visual image of being on the running machine.

So the question is what effects would this hyper-activation have on the autonomic nervous system and what kind of cognitive psychological or physiological consequences might that have for the patient? And what might modulate those consequences?

DR WILLIAMS: I think there are a couple of things there. One is that immune activation is a feature of untreated chronic infection and that leads to release from the immune system of lots of cytokines which are produced as inflammation. That's bad, generally bad. In

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terms of the autonomic nervous system, definitely like the peripheral nervous system and the central nervous system, it can be affected by HIV.

Neurons are not directly infected by HIV but the support cells that support those neurones are and so you can -- people can get an autonomic neuropathy as well as getting peripheral neuropathy, and so the features of an autonomic neuropathy would be dizziness when you get up or a fast pulse rate and things like that. Certainly those are features that we have -- I have seen in patients with HIV.

In terms of cognitive, it comes back to Graham's description of HIV in the brain and so -- the drugs don't -- how drugs get across the blood brain barrier may be different but definitely if you look at how -- if you look at HIV in the brain in people who died from HIV, HIV definitely affects the brain in terms of the support cells and results in loss of neurones and can affect people's cognition. There's no doubt about that.

PROFESSOR COOKE: I agree completely, but I think the direct link between inflammation and those

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two things I think is less clear, although those two things are definitely recognised complications of HIV and its treatment.

MS SCOTT: What is the norm to do? Is it the norm to do autopsies on all HIV deaths and, if so, when was that the norm and does it remain the norm?

PROFESSOR ANDERSON: It's no longer the norm. There was a time I think early in the epidemic when there were a lot of very important and unanswered questions and people would die without us understanding why and we would ask, if we could ask for an autopsy, to understand better.

I think now we're doing -- I think there are fewer but there was a period of time when there was a real uncertainty about what had happened and trying to find out.

PROFESSOR COOKE: It differs slightly from centre to centre but I think generally there is an ambition still to do autopsies when the cause of death is unclear.

PROFESSOR ANDERSON: Absolutely.

PROFESSOR COOKE: Partly for the benefit of learning and knowledge, partly for the benefit of family,

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and there are still conditions that are emerging that we still need to learn about, so it's definitely something that's often requested although I think actually progressing to autopsy is less common than it used to be.

MS SCOTT: What is known about the prevalence of HIV infection in, first of all, the United Kingdom population and, secondly, the UK blood donor population since 1970? Are you able to answer those questions?

PROFESSOR ANDERSON: I don't know the date of the blood donor so --

MS EDWARDS: Blood donors?

MS SCOTT: The UK population and the UK blood donor population.

PROFESSOR COOKE: I think we have a figure in the report. I think the figure quoted here is -- no, that is C ... there's a figure in the report I think if someone could find it.

PROFESSOR ANDERSON: The thing I think I would emphasise here is the prevalence of HIV is very variable across the UK, so there are areas where the prevalence is high and that is considered to be greater than 2 per 1,000 population, areas where it's very high where it's greater than 5

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per 1,000 population, but if you take the generality or the average across the UK, then that's lower.

But I think what's important is looking at each particular area because things change very dramatically. The centre of London is quite different from a rural population outside London, for example, so there are some very clear prevalence diagrams from Public Health England where the exact prevalence can be seen. I think those will have been mapped. I'm not sure they have gone back to the -- we would have to look back. I think their records began in about '88/89.

PROFESSOR TUDOR-WILLIAMS: Yes, I think so.

PROFESSOR ANDERSON: But Public Health England are the guardians of that data.

PROFESSOR COOKE: I think the figure we have in the report for the prevalence in first time donors is 0.03 per cent and I just need to check that because I think there might be a typo in the report which we will check in relation to HCV. That is I think the figure for HIV.

PROFESSOR ANDERSON: In terms of, just going back to the prevalence in our supplementary report we

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have been asked some very specific questions on datasets, what is known, where it is, and we will put this into there.

PROFESSOR TUDOR-WILLIAMS: The other source of data is from the national surveillance of HIV in pregnancy and childhood, the NHS -- there's a website that is very accessible that documents all of the seroprevalence rates and, as Jane says, these vary considerably across the nation.

MS SCOTT: Just two more questions. Do you know what the death rates are for babies infected perinatally? So those that would have been infected perinatally.

PROFESSOR TUDOR-WILLIAMS: Yes, I mean, I can tell you the death rates from cohort studies for the perinatal cohorts in Europe were published, natural history data, modified by a little bit of AZT use, but published in about 1996 showed that 15 per cent of the perinatal infected children were dead by the age of 6, whereas the same analysis performed in Malawi showed that 15 per cent of the children were still alive at age 3 so, again, it comes back to all the other co-morbidities that children around the world with HIV are facing, but in Europe the overall

survival rate was about 85 per cent at the age of 6.

MS SCOTT: Are you aware of any studies on the infected blood community? So those that have been infected with HIV through blood and blood products?

PROFESSOR ANDERSON: We are. We have referenced those in the report and I think tomorrow you will be able to get more detail from the team, the expert panel. We have put this in.

MS SCOTT: We can pick that up tomorrow.

PROFESSOR ANDERSON: Yes, the author of that particular point will be on the panel tomorrow.

MS SCOTT: The second part of that question is are you aware of any studies on the stigma -- on those living with HIV for long-term, the consequences of that, and in particular in relation to stigma.

PROFESSOR ANDERSON: Long-term ...?

MS SCOTT: The long-term consequences of living with HIV.

PROFESSOR ANDERSON: As whether people experience more stigma or less stigma or the impact of stigma in the long term?

MS SCOTT: May I just turn behind me because I am

not quite sure. *(Pause)*

I think there are two parts to that second part of the question. So I think studies on stigma in HIV and studies on the long-term consequences of living with HIV.

PROFESSOR ANDERSON: So the long-term consequences of HIV, there are a number of studies ongoing at the moment and I think there's a couple with particular relevance. One is called the POPPY Study, which is looking at people who are both older with HIV and people who are older who do not have HIV, and the data that's coming from that is able to have a very close look at the differences between people who are living with HIV and getting older and the people who aren't. Data is coming from that study now and that's being co-ordinated by Imperial and UCL.

In terms of stigma, there's a lot of work going on, I think one of the things I would say is that we are very well aware that HIV-associated stigma remains one of the key blocks to long-term good health because of some of the things we've discussed. We know that people are still not taking HIV tests early enough and so we're seeing ill health from late

diagnosis, which is associated with stigma. We know that people are avoiding medical care, so stigma is having a direct impact on well-being.

PROFESSOR COOKE: One of the things we were discussing outside was that I think as HIV is seen less as a public health crisis and more as a chronic infection increasingly in elderly populations, it's getting harder to motivate for resource for the kind of studies that will answer those questions. We have seen a recent example of where funding has ceased for the big UK cohort study which gave us a lot of this information.

MS SCOTT: Those I think are the end of the questions that I have but can I just turn behind me to see if anything arose after the break.

No, I don't think so. No further questions.

SIR BRIAN LANGSTAFF: There's no question from me. When you were talking about advice, advising someone about their infection, you described the advice and learning as a process.

I have to say that you collectively have contributed very much to what has been a process of learning for me. It's part of a process, in

no way have I finished, but I must thank you very much for that. You might like to know that in the breaks a number of people have been speaking very highly, and entirely correctly so in my view, of the expertise and the empathy that you have shown.

One of them described you as a fantastic group of experts. Another said that they were very grateful that they felt that you had, in what you had to say, acknowledged the symptoms which they have lived with for years, something which plainly is of real value.

Can I thank you for that besides thanking you for having made the time to come here and share your expertise and indeed to give yourselves the task of going on to answer the supplementary questions and be available for any further expert advice that we may wish from you. Thank you.

It is 10.30 tomorrow and we will be examining bleeding disorders, will we?

MS SCOTT: Yes.

SIR BRIAN LANGSTAFF: So 10.30.

(4.45 pm)

(Adjourned until 10.30 am the following day)