

Expert Report to the Infected Blood Inquiry: HIV

January 2020

A white circular logo containing the text "Infected Blood Inquiry" in a bold, sans-serif font, stacked in three lines.

**Infected
Blood
Inquiry**



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Introduction

This is the first of two documents compiled by the clinical group in response to the questions posed in the Letters of Instruction of September and December 2019. The document is set out in a way that follows a progression through the natural history, diagnosis and treatment of HIV, which means that the points are not always in the same numerical order and supplementary points are inserted where they appear to fit best. The numerical identifier of each point is clearly identified within the text. Because certain questions in the Letters of Instruction may have areas of overlap, the text of some responses has been duplicated across sections.

The document is written with reference to the situation in the UK. The British HIV Association (BHIVA) has developed an extensive library of evidence-based guidelines and standards which are the quality benchmark for diagnosis, treatment and care for people living with and affected by HIV in the UK. There is also national guidance from, among others, the British Association of Sexual Health and HIV (BASHH), Public Health England (PHE), NHS England and the National Institute for Health and Care Excellence (NICE). These are key sources that are frequently cited within this report.

The terminology and language used throughout this document aim to be consistent with the UNAIDS (2015)¹ recommendations.

What is (a) HIV and (b) AIDS? (Point 14.1)

HIV (human immunodeficiency virus) is a virus that preferentially attacks and kills the particular cells (the CD4 T lymphocytes) that control the immune system and thereby allow the body to fight infection. By damaging the immune system, HIV makes a person vulnerable to life-threatening infections and cancers. If left untreated, HIV can lead to the condition AIDS (acquired immune deficiency syndrome). HIV is the cause of one of humanity's most serious and persistent epidemics. Since the first reports of AIDS in 1981, more than 78 million people are estimated to have been infected with HIV and 39 million people have died. At least 36.9 million people worldwide are living with HIV infection. Today, with the knowledge and tools that are now at our disposal, HIV is a completely preventable infection.

Identified in 1983, HIV belongs to a virus family known as 'retroviruses', which use the enzyme reverse transcriptase to turn viral RNA into DNA which can then be merged into the genetic material of the host cell. HIV exists in two types – HIV-1 and HIV-2 – with HIV-1 being responsible for the majority of HIV

infections worldwide. HIV-2 infection is found largely in West Africa with some spread to Europe, particularly France and Portugal. Both HIVs result from a number of different cross-species transmissions of simian immunodeficiency viruses (SIVs) that infect African primates. Unless otherwise noted, the term ‘HIV’ refers to HIV-1.

HIV-1 is classified into four distinct subtypes – M, N, O and P – each reflecting a specific cross-species transmission. The transmission event that involved SIV crossing from chimpanzees to human beings in south-eastern Cameroon is thought to have given rise to HIV-1 group M, which is the major subtype accounting for 98% of global infections and the principal cause of the AIDS pandemic. Within subtype M, there is further viral diversity with different ‘clades’, denoted A–K, which have geographical differences in origin and distribution.²

HIV-1 and 2 are both transmitted horizontally through direct contact with body fluids, including blood, semen and vaginal fluids, or vertically from a mother who has HIV-1 to her child during pregnancy, delivery or through breast milk. The majority of HIV infections are transmitted sexually via semen, cervical secretions and blood.

Once acquired, the human body cannot get rid of HIV and no effective HIV cure exists, which means that HIV is present for life. However, by consistently taking anti-

HIV medicine (called ‘antiretroviral therapy’ or ‘ART’), people with HIV can live long and healthy lives and become non-infectious, preventing transmission of HIV to their sexual partners and children.

Changes and mutations in HIV (Point 14.3)

The human immunodeficiency virus (HIV) evolves rapidly owing to the combined activity of error-prone reverse transcriptase, recombination and short generation times, leading to extensive viral diversity both within and between hosts. This diversity is a major contributing factor in the failure of the immune system to eradicate the virus, and has important implications for the development of suitable drugs and vaccines to combat infection.³ This also has obvious biological implications as untreated patients eventually lose control over the virus and progress to AIDS.

The rate of progression to AIDS is determined by the level of HIV replication and host factors (see section on Natural History on p.5). Some HIV mutations that develop while a person is taking HIV medicines can lead to drug-resistant strains of HIV. Once drug resistance develops, medicines that previously controlled a person’s HIV are no longer as effective. In other words, the HIV medicines cannot prevent the drug-resistant HIV from multiplying. Drug resistance can cause HIV treatment to fail. Drug-resistant HIV can be transmitted from person to person or develop

after a person starts taking HIV medicines (see Point 14.11b).

Human immunodeficiency virus (HIV)

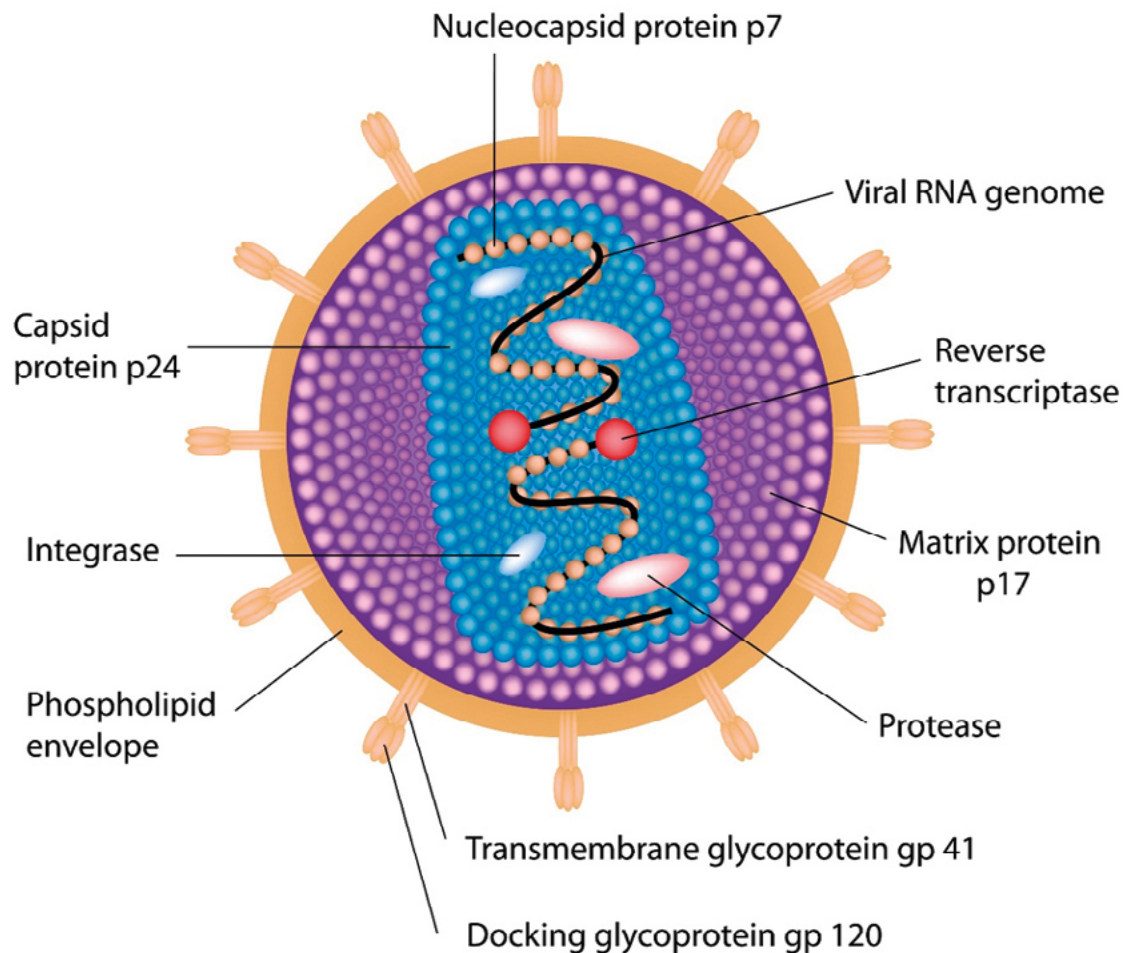


Figure 1a: The structure of HIV

Source: Dreamstime, *Structure of HIV*, accessed 28 January 2020, available at <<https://www.dreamstime.com/stock-photography-structure-hiv-image23617032>>.

The HIV lifecycle

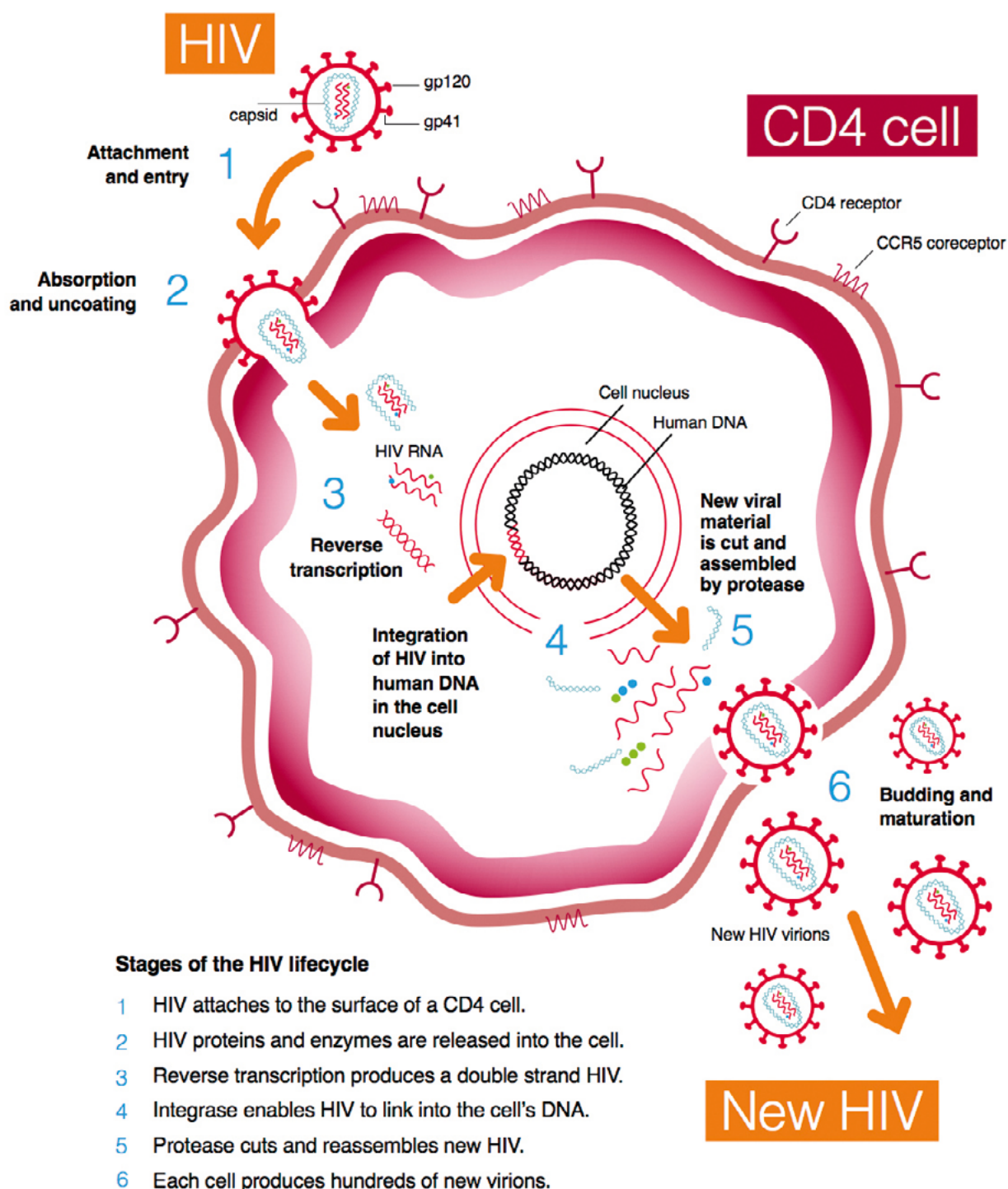


Figure 1b: The HIV lifecycle

Source: Collins, S 2019, *The HIV Lifecycle*, accessed 28 January 2020, available at <<http://i-base.info/guides/wp-content/uploads/2017/06/ART-in-pictures-2-HIV-lifecycle.png>>.

What is AIDS?

AIDS stands for 'Acquired Immune Deficiency Syndrome' and is a set of illnesses that occur at the late stage of HIV infection. It is diagnosed when the body's immune system is so severely damaged by HIV that serious infections can no longer be controlled or resisted. AIDS and HIV are not the same – AIDS is the clinical condition of which HIV is the causative agent.

A person with HIV is considered to have AIDS when:

- the number of CD4 cells falls below 200 cells per cubic millilitre of blood (200 cells/mm³) (in someone with a healthy immune system, CD4 counts are between 500 and 1,600 cells/mm³); or
- the person develops one or more AIDS-defining conditions or opportunistic infections regardless of their CD4 count; AIDS-defining conditions are listed in the US Centers for Disease Control and Prevention (CDC)'s list of diagnostic criteria for AIDS and include opportunistic infections and cancers that are life-threatening in a person with HIV; this is the clinical definition that is most frequently used in the UK.

More detail can be found on the stages and classification of HIV in Points 14.6, 14.9 and 14.13.

Today in the UK, most people with HIV do not develop AIDS because they start taking effective medication that treats HIV, anti-retroviral therapy (ART), before

the immune system is badly damaged. Effective daily ART stops the activity and progression of HIV. Without ART, people with AIDS typically live for about three years. Once someone has an opportunistic illness, life expectancy without treatment falls to about one year. ART can still help people at this stage of HIV infection, and can be life-saving. However, people who start ART soon after they acquire HIV experience more benefit – thus the importance of HIV testing, early diagnosis and rapid initiation of therapy.

Terminology

- The expression ‘HIV/AIDS’ should be avoided because it is imprecise and can cause confusion. Most people in the UK who are living with HIV do not have AIDS.
- The term ‘HIV virus’ is tautological – HIV stands for ‘human immunodeficiency virus’, so there is no need to repeat the word ‘virus’.
- The term ‘AIDS virus’ is still used by the general press. AIDS is a clinical syndrome and it is incorrect to refer to an ‘AIDS virus’: HIV is the virus that leads to the development of AIDS.

Previously used terminology

- Lymphadenopathy-associated virus (LAV):⁴ this terminology was used to first describe the virus when it was isolated in France in 1983.

- Human T-lymphotropic virus type III (HTLV-III) was used to describe the virus isolated in the USA in 1984.⁵
- With time, it became clear that LAV and HTLV-III were the same virus. Two compound names (HTLV-III/LAV and LAV/HTLV-III) were used during this period. The terms ‘immunodeficiency-associated virus (IDAV)’ and ‘AIDS-associated retrovirus (ARV)’ were also being used.
- In 1986, the International Committee on the Taxonomy of Viruses, noting the need to clarify the terminology, recommended the term ‘Human Immunodeficiency Virus’ (HIV).⁶
- The first report of five patients with pneumocystis carinii pneumonia in the USA was published on 5 June 1981.⁷ In June 1982, it was first suggested that the cause of this immune deficiency was sexual and the syndrome was initially called ‘Gay-Related Immune Deficiency’ (or ‘GRID’).⁸
- In September 1982, the CDC first used the term ‘Acquired Immune Deficiency Syndrome (AIDS)’.⁹

Classification and stages of infection (Point 14.9 partial)

The natural history of untreated HIV infection is divided into early, chronic and advanced stages which are associated with progressively worsening immunodeficiency:

- Early infection (the first 6 months) includes acquisition of infection and acute/primary HIV infection (see Point 14.6).
- Chronic infection may be asymptomatic (see Point 14.7) or associated with a variety of symptoms and conditions which do not meet the defining criteria for AIDS.
- Advanced infection includes Acquired Immunodeficiency Syndrome (AIDS), which is defined by a CD4 count below 200 or the diagnosis of an AIDS-defining clinical condition irrespective of CD4 count (see Table 1).

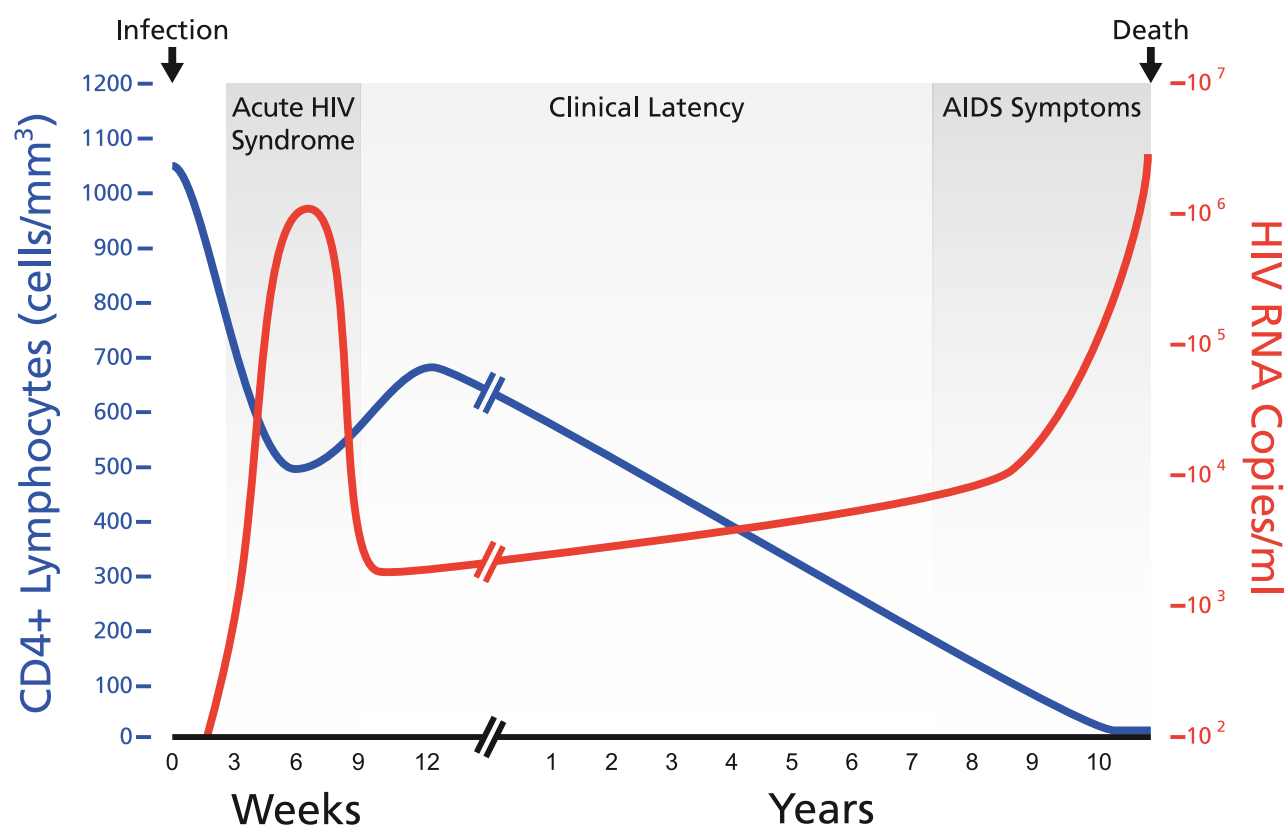


Figure 2: The natural course of HIV infection

Source: Wikimedia Commons, *HIV-Timecourse*, accessed 28 January 2020, available at https://commons.wikimedia.org/wiki/File:HIV-timecourse_simple.svg.

Classification of the stages of HIV infection

Standardised case definitions of HIV infection have been established by The World Health Organization (WHO)¹⁰ and by the US Centers for Disease Control and Prevention (CDC) classification.^{11,12} Their key application is public health monitoring and surveillance rather than clinical diagnostic tools. The most frequently used system is Centers for Disease Control (CDC) 1993 classification. Although the CDC classification was updated in 2014 the 1993 CDC classification remains is the most frequently used and is described below. The most recent (2014) CDC classification has 5 stages (Stages 0 – 4 or unknown), includes a combination of HIV positive laboratory results, the CD4 count / percentage, and the presence of clinical stage 3 defining conditions.¹³

Symptomatic HIV infection includes conditions listed in either categories B or C, however only the conditions in category C are considered AIDS defining.

In the UK the definition of AIDS requires the presence of an AIDS defining clinical condition. (category C list). A CD4 count below 200 alone is not AIDS defining.

In the USA a CD4 count below 200 is AIDS defining whether or not a category C condition is present.

Table 1: Summary of Centers for Disease Control and Prevention’s ‘1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults’¹¹

Absolute CD4 count (/mm³)	A Asymptomatic <i>or</i> persistent generalised lymphadenopathy <i>or</i> acute, symptomatic (primary) HIV infection	B HIV-related conditions that are not A or C	C Clinical conditions listed in AIDS surveillance case definition
>500	A1	B1	C1
200–499	A2	B2	C2
<200	A3	B3	C3

CLINICAL CATEGORY A	CLINICAL CATEGORY B	CLINICAL CATEGORY C AIDS DEFINING DISEASES
<p>Asymptomatic HIV infection</p> <p>Acute, symptomatic (primary) HIV infection</p> <p>Persistent generalised lymphadenopathy (PGL)</p>	<p>Symptoms or signs of diseases that do not fall into Category C but are associated with a disturbed cellular immunity. Among these are:</p> <ul style="list-style-type: none"> • Bacillary angiomatosis • Infections of the pelvis – in particular, complications of fallopian tube or ovarian abscesses • Herpes zoster in the case of more than one dermatome or recurrence in the same dermatome • Idiopathic thrombocytopenic purpura • Constitutional symptoms like fever or diarrhoea lasting >1 month • Listeriosis 	<p>AIDS defining diseases:</p> <ul style="list-style-type: none"> • Candidiasis of the bronchia, trachea or lungs • Esophageal candidiasis • Cytomegalovirus (CMV) infections (except liver, spleen and lymph nodes) • CMV retinitis (with loss of vision) • Encephalopathy, HIV-related • Herpes simplex infections: chronic ulcer (>1 month) or bronchitis, pneumonia, esophagitis • Histoplasmosis, disseminated or extrapulmonary • Isosporiasis, chronic, intestinal, duration >1 month • Kaposi's sarcoma • Coccidioidomycosis, disseminated or extrapulmonary • Cryptococcosis, extrapulmonary

CLINICAL CATEGORY A	CLINICAL CATEGORY B	CLINICAL CATEGORY C AIDS DEFINING DISEASES
	<ul style="list-style-type: none"> • • Oral hairy leukoplakia (OHL) • Oropharyngeal candidiasis (oral thrush) • Vulvovaginal candidiasis, either chronic (>1 month) or difficult to treat • Cervical dysplasia or carcinoma in situ • Peripheral neuropathy 	<ul style="list-style-type: none"> • Cryptosporidiosis, chronic, intestinal, duration >1 month • Lymphoma, Burkitt • Lymphoma, immunoblastic • Lymphoma, primary CNS • <i>Mycobacterium avium complex</i> or <i>M. kansasii</i>, disseminated or extrapulmonary • Mycobacterium, other or not identified species • <i>Pneumocystis pneumonia</i> (PCP) • Pneumonia, bacterial, recurrent (>2 within a year) • Progressive multifocal leukoencephalopathy • Salmonella sepsis, recurring • Tuberculosis • Toxoplasmosis, cerebral • Wasting syndrome • Cervix carcinoma, invasive

HIV timeline with a focus on the situation in the UK (Point 14.2)

- **1981:** The Morbidity and Mortality Weekly Report (MMWR), published by the Centers for Disease Control and Prevention (CDC), describes pneumocystis carinii pneumonia in five men who have sex with men (MSM) in Los Angeles, California, USA, documenting for the first time what became known as ‘AIDS’. MMWR also reports additional diagnoses of pneumocystis carinii pneumonia, other opportunistic infections and Kaposi Sarcoma in MSM from New York City and California.¹⁴
- **1981:** The first recorded case of AIDS in the UK.¹⁵
- **1982:** The term ‘AIDS’ is used for the first time; a definition is agreed and a proforma for collecting data on each case – the AIDS surveillance form – is introduced in the USA and for use worldwide.⁹
- **1982:** Terry Higgins dies from AIDS in the UK – leading to the establishment of the Terence Higgins Trust.¹⁶
- **1983:** Lymphadenopathy-associated virus (LAV) is described in France as an accomplishment for which French scientists received the Nobel Prize in Medicine in 2008.^{4, 17, 18}
- **1984:** Human T-lymphotropic virus type III (HTLV-III) is identified in the USA by Robert Gallo.⁵

- **1984:** Project SIDA starts work in Kinshasa DRC, a Zairian-American-Belgian research programme that shed much light on the emerging epidemic.¹⁹
- **1985:** First World AIDS Conference held in Atlanta.²⁰
- **1985:** Slim disease associated with HTLV III reported in Uganda.²¹
- **1985:** The first commercial blood test detecting HTLV III antibodies in the blood (an indication of infection) is licensed for use in the UK.^{22,23}
- **1985:** Fifty per cent of samples from people who inject drugs in Edinburgh are found to be HTLV III antibody positive; Edinburgh is labelled by the press as the AIDS capital of Europe.²⁴
- **1985:** The UK's Expert Advisory Group on AIDS is established by Sir Donald Acheson, Chief Medical Officer of England.²⁵
- **1985:** The UK's national infectious disease surveillance centres, having introduced the AIDS surveillance form in 1982, establish HIV antibody diagnosis reporting systems to determine the characteristics and extent of infection. It becomes apparent that infection is being transmitted through unprotected sexual intercourse particularly among MSM, but appreciable numbers of heterosexually acquired infections are also being diagnosed especially among the sexual partners of people who inject drugs and people from sub-Saharan Africa. A high proportion of people who had

received blood factor, some people who had been transfused with blood, and a small but appreciable proportion of babies born to mothers with HIV are found to be infected.²⁶

- **1986:** The International Committee on the Taxonomy of Viruses recommended the term ‘Human Immunodeficiency Virus’ (HIV).⁶
- **1986:** The UK Government’s Cabinet Committee on AIDS is established.²⁶
- **1980s (mid):** Heat treatment for blood factor is introduced.
- **1987:** The National AIDS Trust (NAT) is founded.²⁷
- **1987:** Diana, Princess of Wales, opens a new ward at the Middlesex Hospital for the treatment of patients with HIV and shakes the hands of patients with AIDS without the use of gloves.²⁸
- **1987:** The UK Government launches ‘AIDS: Don’t Die of Ignorance’ – a major public information campaign with leaflets delivered to every household in the UK. This campaign is championed by the UK’s Secretary of State for Health, Norman Fowler.²⁹
- **1987:** The UK Medical Research Council (MRC) initiates a directed programme aimed at developing vaccines for prevention and drugs for the treatment of HIV infection and AIDS.³⁰
- **1987-90:** New funding for interventions to prevent, and manage people with HIV infection is made available by the UK Government.³¹

- **1987:** Approval and introduction of AZT (Zidovudine) for the treatment of people with severe HIV disease.³²
- **1987:** The first needle and syringe exchange schemes are introduced in the UK to prevent the transmission of HIV among people who inject drugs. Between 1987 and the early 1990s, harm reduction services – particularly those involving needle and syringe exchange and opiate replacement therapy – become established throughout the UK.^{33, 34}
- **1989-90:** Implementation of the UK's unlinked anonymous HIV testing programme to ascertain the prevalence of HIV among different population groups by the Communicable Diseases Surveillance Centre in England and the Communicable Disease (Scotland) Unit.³⁵
- **1990:** Launch of the National Survey of Sexual Attitudes and Lifestyles in response to the emerging HIV epidemic in the UK.³⁶
- **1990:** The BBC soap opera 'EastEnders' runs a storyline involving a major character who has HIV.³⁷
- **1991:** Freddie Mercury of the band, 'Queen', dies of AIDS.³⁸
- **1991:** World AIDS Day is established by the World Health Organization, (1 December).³⁹
- **1991:** The establishment of the UK Advisory Panel for Healthcare Workers Infected with HIV (the

Panel extended its remit in 1993 to include other blood-borne viruses).⁴⁰

- **1992:** The UK Government's 'Health of the Nation' report sets targets for improving health and five key areas including HIV/AIDS and sexual health.^{41, 42}
- **1993:** The MRC's Committee on the Epidemiological Study of AIDS is established.⁴³
- **1993:** The first major outbreak of HIV in a UK prison: HMP Glenochil, Stirlingshire.⁴⁴
- **1994:** The initial use of AZT in HIV-positive pregnant women is shown to prevent mother-to-child transmission of infection.⁴⁵
- **1994:** In the UK, 27,000 people have been diagnosed with HIV; of those, 11,500 have presented with AIDS and 8,900 have died.⁴⁶
- **1995:** The establishment of the British HIV Association, an organisation representing professionals in HIV care: responsible for undertaking national audits, setting clinical standards, developing clinical guidelines and promoting education and research.⁴⁷
- **1996:** Proof of concept that Highly Active Antiretroviral Therapy (HAART) can fully suppress HIV activity is presented at Vancouver International Aids Society conference.⁴⁸
- **1996:** Availability and introduction of (HAART) in the UK.^{49, 50}

- **1997-8:** A rapid decline in the number of cases of AIDS and AIDS-related deaths as a consequence of the use of HAART is observed in the UK.^{51, 52}
- **1999:** All pregnant women in the UK are offered HIV screening as part of routine antenatal care.⁵³
- **2000:** The UN General Assembly adopts combating HIV/AIDS as one of the Millennium Development Goals.⁵⁴
- **2001:** Establishment of the Global Fund to fight HIV, Tuberculosis and Malaria. Approved by the United Nations in June 2001 and endorsed at the Gleneagles G8 summit that July.⁵⁵
- **2001:** The first national strategy for sexual health and HIV in England is published.⁵⁶
- **2001:** The first successful prosecution of the sexual transmission of disease in the UK: a man from Scotland is convicted for recklessly injuring his former girlfriend by infecting her with HIV.⁵⁷
- **2000s (early):** HIV nucleic acid testing is introduced in blood donor settings.⁵⁸
- **2000-5:** The approach to HIV testing moves successfully from an opt-in to an opt-out one in antenatal and sexual health/genito-urinary medicine clinic settings; HIV test uptake is improved dramatically.⁵⁹
- **2003:** The World Health Organization and UNAIDS launch the '3 by 5' initiative in low- and middle-income countries (3 million people to be treated with Antiretroviral Therapy (ART) by 2005). The

impact of this initiative would be experienced worldwide.⁶⁰

- **2003:** The US President's Emergency Plan for AIDS Relief (PEPFAR) launches.⁶¹
- **2005:** The Disability Discrimination Act is passed and gives legal protection against the discrimination of people with HIV in the UK.⁶²
- **2007:** The UK Department of Health publishes guidelines making it mandatory for healthcare workers undertaking exposure-prone procedures for the first time to be negative for HIV, hepatitis B and hepatitis C.⁶³
- **2009:** Timothy Brown ('The Berlin Patient') is shown to have cleared HIV following a stem cell transplant, raising hopes for a cure.⁶⁴
- **2010:** The Equality Act 2010 qualifies anyone with HIV as disabled and thus gives protection against discrimination.⁶⁵
- **2010:** The USA IPREX study demonstrates oral PrEP (Pre Exposure Prophylaxis) to be effective in reducing HIV acquisition.⁶⁶
- **2011:** Evidence that effective HIV treatment prevents onward transmission, setting the scene for 'treatment as prevention' (HTPN 052).⁶⁷
- **2012:** HIV Prevention England/The Terrence Higgins Trust launches the UK's first 'National HIV Testing' week (November).⁶⁸

- **2012:** HIV treatment made available without charge for everyone in the UK, regardless of citizenship or immigration status.⁶⁹
- **2013:** The British HIV Association publishes a position statement recommending the use of HAART to reduce HIV transmission (i.e. HIV treatment, potentially, has population as well as individual benefits).⁷⁰
- **2014:** The Joint United Nations Programme on HIV and AIDS (UNAIDS) and partners set the ‘90-90-90 targets’ aiming to diagnose 90% of all HIV-positive people, provide ART) for 90% of those diagnosed and achieve viral suppression for 90% of those treated, by 2020.⁷¹
- **2013-15:** UNAIDS and WHO policy to treat all people diagnosed with HIV, regardless of their HIV-disease stage, is implemented across the UK.^{72, 73}
- **2013:** Implementation of the Health and Social Care Act 2012, establishing NHS England and Public Health England, and transferring commissioning responsibilities for the HIV pathway from a single organisation (the NHS) across multiple agencies, including local authorities, clinical commissioning groups and NHS specialist commissioners.⁷⁴
- **2015 PROUD** study reports: HIV PrEP shows an 86% reduction in new HIV infections among MSM in the UK.⁷⁵

- **2016:** NHS England asserts it is not legally able to commission HIV PrEP. A judicial review brought by the National AIDS Trust and the Local Government Association and High Court determined that NHS England has the power to provide PrEP.⁷⁶
- **2017:** A three-year implementation trial of HIV PrEP to evaluate the effectiveness of providing HIV therapy to people at high risk of acquiring HIV (especially MSM) begins across sexual health clinics in England. In Scotland and Wales, HIV PrEP is licensed for use and made available through the NHS to eligible people.^{77, 78, 79}
- **2017:** The first reported fall in new HIV diagnoses amongst gay men in London since reporting began. Result of the combination of increased HIV testing, rapid initiation of ART and PrEP.⁸⁰
- **2018:** Since the start of the epidemic 160,493 people have been diagnosed with HIV across the UK. Of these 19, 610 presented with AIDS and 24,610 have died.⁴⁶
- **2018:** The UK achieves the UNAIDS 90:90:90 targets (90% of those infected, diagnosed: 90% of those diagnosed, treated: 90% of those treated, virally suppressed).⁸¹
- **2018:** An estimated 104,000 people are living with HIV in the UK.⁸²
- **2018:** Launch of the UK Infected Blood Inquiry.

- **2019:** The UK Minister of Health, Matt Hancock, pledges to end new HIV infections across the UK by 2030.⁸³
- **2019:** The establishment of an independent commission by NAT and the Terrence Higgins Trust, chaired by Dame Inga Beale, to consider approaches to end new HIV transmissions and HIV-attributed deaths in England by 2030.⁸⁴

How is HIV diagnosed? (Point 14.5)

How HIV and AIDS are diagnosed, and how this has changed over the years. Included are descriptions of the tests and procedures used to effect diagnoses, and an analysis of how reliable the various diagnostic tests have been over the years.

Background to diagnostic approaches

Serology

The majority of HIV, hepatitis B and hepatitis C infections are initially diagnosed using enzyme immunoassays (EIAs). These techniques are widely used for screening large groups of people, as they are relatively inexpensive and can be highly automated. These assays are also known as ‘serological assays’ as they are usually performed on blood serum or plasma samples, but may also be performed on capillary/venous whole blood and oral fluid. Other serological assay formats include rapid diagnostic tests (RDTs), chemiluminescence immunoassays and electro-chemiluminescence immunoassays. The most recent assay format is the Chemiluminescent Microparticle Immunoassay (CMIA). Most serological assays are designed to detect specific antibodies which are produced in response to infection but, in the case of hepatitis and HIV, assays have also been designed to look directly at protein components (HBsAg, HCVcoreAg, p24 (HIV)) of the virus, or a

combination of both antigen and antibody (for example, fourth generation HIV assays). The principle of any EIA is that an antigen or antibody which will specifically bind to the complementary antigen or antibody of interest (for example, hepatitis B surface antigen [HBsAg] or hepatitis C antibody) is immobilised on a solid surface – for example, a 96-well plate or a bead. If the antigen or antibody of interest is present in the serum, it will specifically bind to the immobilised complementary antigen/antibody. This can then be detected by using a secondary antibody which specifically binds to the antigen or antibody of interest and which has an enzyme attached to it. A chemical is added to be converted by the enzyme into a colour or a fluorescent or electrochemical signal. The amount of signal produced can be quantified and gives a measure of the amount of antigen or antibody in the blood sample. Between each step, the plate is washed with a mild detergent to remove any antigens or antibodies that are non-specifically bound. This is known as a ‘sandwich ELISA’ or ‘indirect ELISA’ (see Figure 3 below).

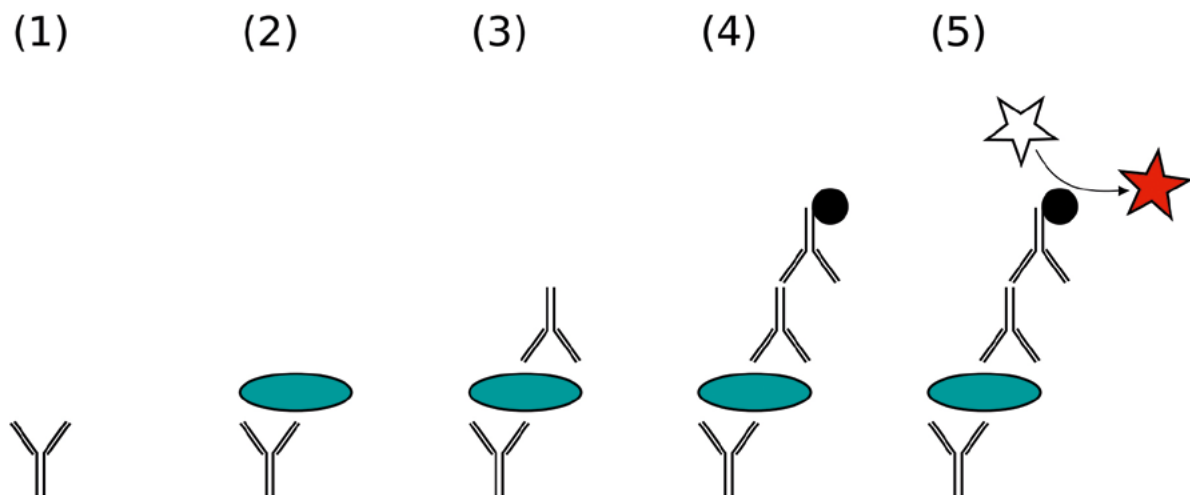


Figure 3: A sandwich ELISA.

Notes:

1. Vinocur JM, 2006 *A Sandwich ELISA*, accessed 28 January 2020, available at <<https://en.wikipedia.org/wiki/ELISA#/media/File:ELISA-sandwich.svg>>.
2. (1) Plate is coated with a capture antibody; (2) sample is added, and any antigen present binds to capture antibody; (3) detecting antibody is added, and binds to antigen; (4) enzyme-linked secondary antibody is added, and binds to detecting antibody; (5) substrate is added, and is converted by enzyme to detectable form.

Nucleic acid testing

The other key group of diagnostic assays for HBV, HCV and HIV are molecular assays, or nucleic acid testing (NAT) – for example, polymerase chain reaction (PCR) or nucleic acid sequence-based amplification that can detect very small quantities of viral nucleic acid (RNA or DNA). As well as detecting the presence of the virus, these assays can provide quantification of the virus in either virus copies/ml or, more recently, in the interest of standardising assays as international units IU/ml). These assays detect DNA or RNA by targeting a specific segment of the virus, which is then amplified. The amplification step enables the detection

of low levels of the virus in the original specimen, which might not otherwise have been detectable. Laboratory-based technologies for NAT require sophisticated equipment, rigorous laboratory conditions and specimen collection, and highly trained staff who can perform precision steps and avoid contamination. NAT technologies are typically used to detect the presence of the virus, and to determine whether the infection is active and the individual would benefit from antiviral treatment. NAT technologies are also used to determine when antiviral treatment should be discontinued (due to non-response or resistance) or to confirm virological cure (HCV) or effective suppression (HBV). These assays are high cost compared with serological assays. Specialist virology laboratories were providing non-commercialised NAT-based assays (qualitative) from the early 1990s, often developed ‘in-house’, with more automated and quantitative assays becoming available in the second half of that decade. More sensitive and highly automated assays using real-time PCR technology have been used routinely since the mid to late 2000s.

Measures of test performance

Key attributes of any diagnostic test are the sensitivity (that is, the extent to which a test correctly identifies those with the disease [true positive rate]) and specificity (that is, the ability of the test to identify those without the disease [true negative rate]). A test with

100% sensitivity correctly identifies all those with the condition of interest; anything less than a sensitivity of 100% will mean that an individual may go undetected (false negative). A test with 100% specificity correctly identifies all those without the condition of interest; anything less than 100% will mean that an individual will be incorrectly diagnosed as being test positive (false positive). In general, screening tests designed for the diagnosis of HBV, HCV and HIV have a high sensitivity so that individuals with the diagnosis are not missed, which is important when such tests are used in the setting of blood donor screening. However, sensitivity and specificity of a test only describe how well the test performs against the gold-standard test for that disease. In order to assess how well a test performs in a particular population, where the prevalence of the disease may vary, it is necessary to understand the positive and negative predictive value of the test. The positive predictive value (PPV) of a test is the probability that, when a person's test result is positive, they truly have the infection/disease, whereas the negative predictive value (NPV) describes the probability that, when a person's test result is negative, they truly do not have the infection/disease. Generally, a higher prevalence of the disease in the population will increase the PPV and decrease the NPV. When a test is applied to a population with a low prevalence of the disease in question, unless the test has 100% specificity, the number of false positive results will be higher than when testing a population with a

high prevalence. It is therefore important to design screening tests with a high sensitivity, and to perform further confirmatory tests with a high specificity before confirming the diagnosis. Before a confirmed diagnosis is made, further confirmatory tests with a high specificity are required. As the sensitivity of EIAs has increased, the window period (the time from infection with the virus to the appearance of measurable virus antigen or antibody) has decreased.

Laboratory diagnosis of HIV infection

Clinical cases of HIV infection and AIDS were first recognised in 1981. The recognition of cases in intravenous drug users, haemophiliacs and infants born to mothers with AIDS suggested a blood-borne as well as a sexually transmitted pathogen. In May 1983, Dr Luc Montagnier of the Pasteur Institute in Paris isolated a virus which he named 'LAV' (lymphadenopathy-associated virus) that he believed to be the causative agent of AIDS. His work, although not fully appreciated at the time, became the basis for the development of tests to detect the virus and its antibodies.

In April 1984, Dr Robert Gallo of the National Institute of Health in the USA and his team of researchers isolated the virus that was the causative agent of AIDS. He named this virus 'HTLV-III' (human T-cell lymphotropic virus). This was the same virus that Dr Montagnier had found and, while at the time

it was announced that the isolation had occurred independently of Dr Montagnier's work, it was later found that Dr Gallo's discovery was based, in part, on a sample of the virus provided by Dr Montagnier's laboratory. Dr Gallo produced a reagent capable of reacting with HTLV-III antibody present in blood serum. He was therefore able to test blood samples for the presence of HTLV-III antibody. A few weeks later, a third scientist, Dr Jay A. Levy of the University of California at Berkeley, also isolated the virus, which he named 'ARV' (AIDS-related virus). Eventually, in 1986, the virus became known as 'HIV' (human immunodeficiency virus), and for convenience that name is used throughout this chapter. Soon after Dr Gallo developed the test for HIV antibody, he shared his expertise and resources with the Canadian government, which developed a similar test at the Laboratory Centre for Disease Control in Ottawa in the summer of 1984. This test was performed on only a limited basis in research laboratories. It was not widely accessible. HIV antibody test kits were licensed and available in the United States at the beginning of March 1985.

In 1984, two methods were commonly used to test blood samples for HIV antibody. The first was an enzyme-linked immunosorbent assay (EIA). No commercial kits were available. Each test had to be made by hand in the laboratory ('in-house' assays). The EIA test was prepared by taking the reagent,

which contained the antigen (the substance capable of inducing an immune response) obtained from inactivated HIV, and coating it on a plate with a number of wells. Although inactivated and non-infectious, the reagent was still able to bind HIV antibodies. The test was performed by diluting serum from a person's blood sample and adding it to one of the wells on the plate. If the person's blood contained HIV antibody, the serum would react with the HIV antigen on the plate. The reaction was made visible by adding reagents that caused a colour change.

The second, or confirmatory, test for identifying HIV antibody available in 1984 was the Western blot test. This is a much more complicated test, more difficult and more expensive. It is performed by separating, using an electric field, 'disrupted' HIV into its various proteins, transferring the proteins to paper, and adding the sample being tested to see whether antibodies in the sample will react with any of the HIV proteins. The various proteins are illustrated on paper as a line each. The completed test resembles a bar code. The western blot test was not confirmatory in the strict sense of the word because, like the EIA test, it tested for HIV antibody rather than the virus itself. It was, however, much more specific because it showed each of the proteins to which a particular sample reacted. Although the Western blot test was widely used, the interpretation of its results did not become standardised until the latter part of the 1980s. The cost

of performing a Western blot test was approximately \$100. By comparison, an EIA test cost about \$4.

The World Health Organization (WHO) recommends replacing Western blotting and line immunoassays with simpler tests in HIV testing services. These simpler tests include RDTs that can be used at the point of care, and EIAs.

These tests get results to the client faster, produce accurate results more often, cost less, can be performed by various cadres of health providers, and can thus facilitate greater access and uptake of HIV testing services among those who need it most.

The first test in an HIV testing strategy and algorithm should have the highest sensitivity, followed by a second and third test of the highest specificity.

There are three main stages following HIV infection in an untreated individual. These are characterised by clinical symptoms and biological markers that also offer the opportunity for use in diagnosis and monitoring using laboratory testing. HIV infection is usually diagnosed by demonstrating the presence of antibodies against HIV-1 or HIV-2 with AIDS being primarily a clinical diagnosis. The clinical manifestation of infection with HIV-1 is the progressive loss of CD-4 positive lymphocytes. The resulting defect in cellular immunity leads to the development of opportunistic infections and malignancies that characterise AIDS.

Acute infection

This phase is characterised by rapid multiplication and spread of the virus in the body, which may take about 2 to 4 weeks following infection. During this stage, there is a burst of viral replication, with shedding and peaking of p24 antigen (Ag) in blood. HIV RNA is also detectable at this stage. During this phase, some people experience flu-like symptoms, such as headache, fever, and rash. The period from infection to the appearance of HIV-Ab (seroconversion) is known as the 'window period'.

Chronic infection

This phase is characterised by continued viral multiplication at low levels, and the person with HIV may not experience any clinical symptoms. The host immune system produces HIV antibodies, which coincides with a decline in the HIV RNA viral load to a steady state. Free p24 antigen levels also fall, as p24 is bound by antibodies to form an antibody-p24 antigen complex. If a patient remains untreated, as viral replication continues, CD4 cells, which serve as host target cells for viral replication, are gradually destroyed, leading to a decline of CD4 cell numbers and the development of symptoms.

AIDS

This phase is characterised by continual viral replication and depletion of CD4 cells, leading

to a weakened host immune system, and is also characterised by opportunistic infections and other clinical symptoms.

The biological markers HIV RNA, p24 antigen, HIV antibodies and CD4 cells are used in laboratory diagnostics for HIV for various applications, including:

- (i) the determination of an individual's infection serostatus (antibodies)
- (ii) distinguishing of recent from long-term infection (antibodies, p24 antigen and HIV RNA)
- (iii) early infant diagnosis using RNA and DNA
- (iv) staging and monitoring of disease progression (CD4)
- (v) identification and monitoring of treatment effectiveness or failure (HIV RNA/virus load)
- (vi) identification of drug resistance mutations.

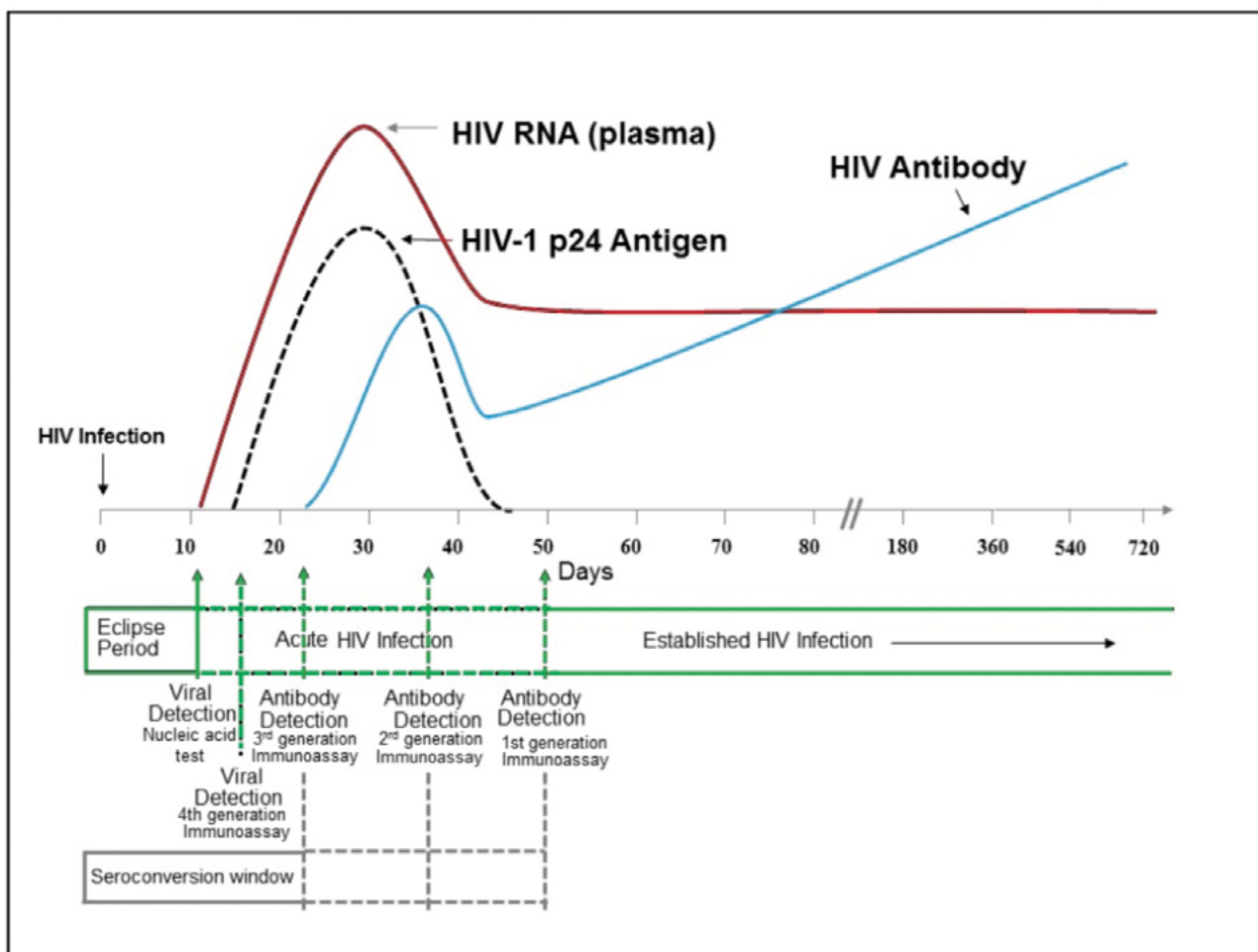


Figure 4: Sequence of appearance of laboratory markers for HIV-1 infection

Note: Units for vertical axis are not noted because their magnitude differs for RNA, p24 antigen, and antibody. Modified from MP Busch, GA Satten (1991) with updated data from Fiebig (2003), Owen (2008), and Masciotra (2011, 2013).

Source: Centers for Disease Control and Prevention 2014, *Laboratory testing for the diagnosis of HIV infection: updated recommendations*, accessed 28 January 2020, available at: <https://stacks.cdc.gov/view/cdc/23447>.

HIV infection is usually diagnosed by demonstrating the presence of antibodies against HIV-1 or HIV-2.

Since the mid-1980s, there have been five generations of EIAs using different antigen preparations and detection chemistries to provide accurate screening for

blood banks and centralised laboratories with a high specimen volume (Figure 5).

The first-generation assays were designed in around 1984 and used antigens derived from whole viral lysates from HIV positive cultures for the detection of IgG antibodies. These assays had a high sensitivity but, due to the presence of impurities in the crude antigen lysate preparations, specificity was as low as 10% (that is, only 1 in 10 positive results were truly positive). Later confirmatory tests with high specificity, such as immunofluorescence assays or Western blotting, were introduced to eliminate false positivity.

In the second-generation assays, synthetic peptides or recombinant proteins derived from the immunodominant regions (IDR) of HIV-1 proteins and the gp36 protein of HIV-2 were used to increase sensitivity and reduce false positivity.

The third-generation assays, such as the Genetic Systems HIV-1/HIV-2 Plus O EIA, used a sandwich format and a variety of antigens to capture HIV-1 and HIV-2 antibodies in serum. These antigens included recombinant p24, gp160 derived from HIV-1 group M, a recombinant peptide from HIV-2 gp36 IDR, and a synthetic peptide from HIV-1 group O. In addition to IgG, the third-generation assays also detected early HIV-1 IgM antibodies and further reduced the window period.

The fourth generation EIAs, such as the Abbott Architect HIV Ag/Ab Combo assay, use fully automated CMIA technology to simultaneously detect HIV-1 p24 antigen and antibodies to HIV-1 (groups M, N and O) and HIV-2. The detection of p24 antigen shortens the window period and increases the chances of early detection of HIV infection. Instruments such as the Abbott Architect provide random-access high-throughput capability so that specimens can be rapidly tested on arrival in the laboratory with results in 30 minutes.

Fifth-generation EIAs, such as the Bio-Rad BioPlex 2200 HIV Ag-Ab assay, use multiple sets of magnetic beads coated with p24 monoclonal antibodies and epitopes specific for HIV-1 (groups M, N and O) and HIV-2 (42), and allow identification of each individual component of the assay. This facilitates identification of people acutely infected with p24 antigen in the window period in a single test. Individuals with HIV-1 or HIV-2 can also be identified for quick confirmation and linked to HIV-1- or HIV-2-specific ART.

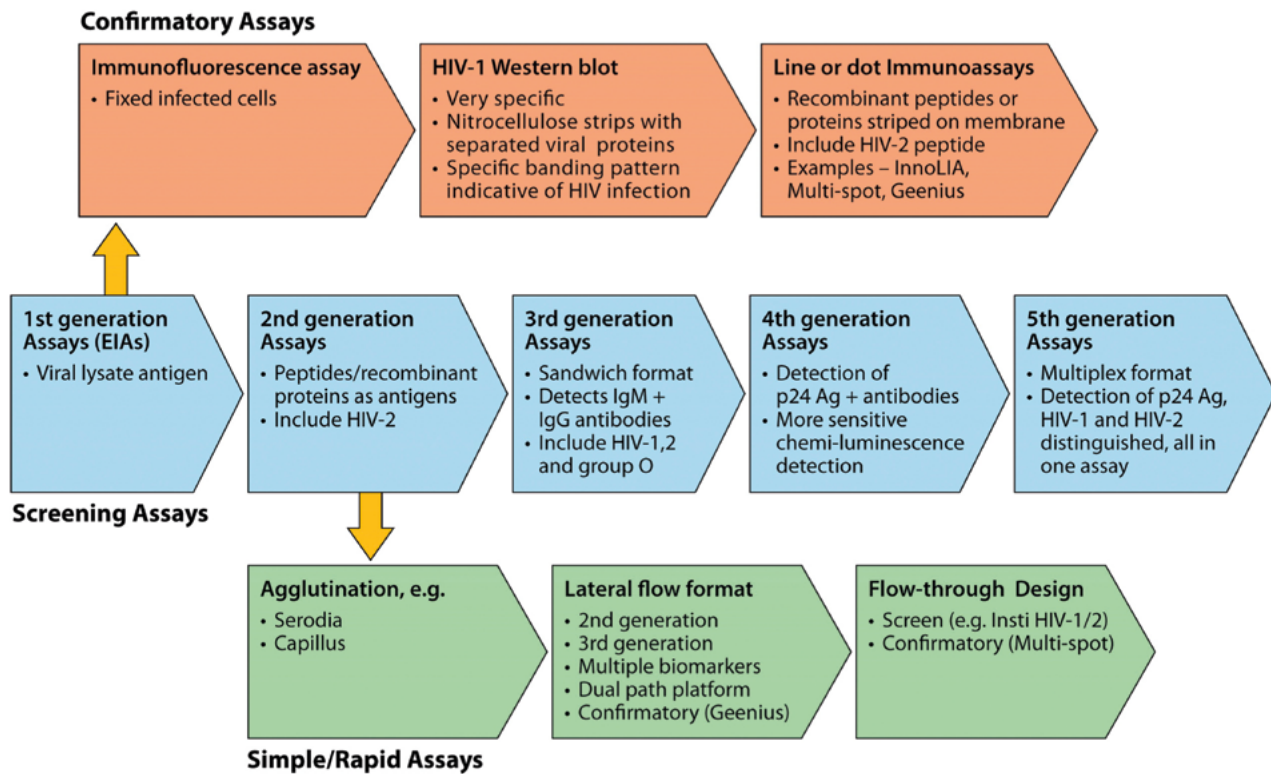


Figure 5: Generations of EIAs for primary HIV infection diagnosis.

Note: Historical evolution of serologic assays for HIV diagnosis. Shown are five generations of screening assays using an EIA format for high-throughput processing. Supplemental assays for confirmation of infection used immunofluorescence, WB, and, more recently, simple line or dot immunoassays. Rapid assays for POC testing were initially agglutination tests and later of a lateral flow format and flowthrough design.

Source: Parekh, BS, Ou CY, Fonjungo PN et al. 2018, 'Diagnosis of Human Immunodeficiency Virus Infection', *Clinical Microbiology Reviews* 32 (1) e00064-18, DOI: [10.1128/CMR.00064-18](https://doi.org/10.1128/CMR.00064-18).

Testing for HIV: approaches in the UK

In 2017 8% of those living with HIV in the UK were unaware of their diagnosis, a fall from 24% in 2013. 43% of people newly diagnosed in the UK in 2017 were diagnosed late that is, they had a CD4 count below <350 cells/mm³ and in 33%, the CD4 count

was <200 cells/mm³, putting them at high risk of HIV-associated pathology.⁸⁵

Given the benefits of treatment of HIV, both to an individual's health and to the wider public health, best outcomes depend upon ensuring that all those with HIV are diagnosed promptly and can rapidly access treatment and care. People who test HIV negative and who remain at risk should be able to access appropriate combination prevention interventions, including pre-exposure prophylaxis [PrEP]) that will allow them to avoid future acquisition. For those at particular risk repeat testing is critically important in ensuring early diagnosis and rapid initiation of therapy. Current approaches aim to expand and normalise HIV testing and avoid exceptionilising the condition. Ongoing barriers to testing include lack of knowledge / information, HIV associated stigma and reluctance to offer testing by healthcare professionals.

UpToDate best practice approaches to HIV testing have been published by NICE and Public Health England.⁸⁶ Latest testing guidance (at the time of writing in still consultation draft form) is available from the British HIV Association (BHIVA) the British Association for Sexual Health and HIV (BASHH) and the British Infection Association (BIA).⁸⁷ In summary all healthcare workers should be able to offer an HIV test in their setting. 'Opt-out' testing, whereby attendees are given information that they will be automatically tested unless they actively decline, aims to increase

coverage and normalise HIV testing. Opt-out models of testing in acute care settings have been shown to be acceptable, feasible and, with appropriate resources, sustainable. Specific pre-test discussion is not required however GMC good practice for any medical intervention should be followed, i.e. individuals should be made aware that they will be tested for HIV and informed how they will receive their result; for clinical settings, opt-out testing is the most effective method to increase testing coverage.

Although a majority of new HIV diagnoses are made within sexual health and genitourinary medicine services an increasing proportion are made in primary care and other clinical and community settings. In 2016 where data are available (n=240,757), GUM clinics tested the greatest proportion of individuals for HIV (49.3%), with a further 18.9% tested in general practice, and 10.8% tested in other known hospital wards. The highest proportion of positive tests were among specialist HIV services, unspecified wards and specialist liver services (31.9%, 7.1% and 1.6% respectively).⁸⁸

In all settings, irrespective of who is delivering the testing, there should be clear, agreed pathways to HIV treatment and care services delivering timely linkage to care. For those testing negative who remain at risk there should be clear pathways to prevention services.

HIV testing is recommended for:⁸⁷

- People belonging to groups at increased risk of testing HIV positive (e.g. men who have sex with men [MSM], Female sexual contacts of MSM, People reporting current or prior injecting drug use; Sex workers; Trans women; people from countries with high HIV seroprevalence and People reporting sexual contact with anyone from a country with high diagnosed seroprevalence regardless of where contact occurs, Trans men; Heterosexuals who have changed sexual partner(s);
- People attending health services associated with increased risk of HIV (e.g. sexual health services, tuberculosis [TB] clinics and addiction and substance misuse services, Termination of pregnancy services); healthcare services for hepatitis B and C, TB and lymphoma;
- All people presenting with symptoms and/or signs consistent with an HIV indicator condition; Individuals who decline on first offer should have at least one repeat offer made at a subsequent visit;
- People accessing healthcare in areas with high (if undergoing venepuncture) and extremely high (all attendees) diagnosed HIV seroprevalence. (High defined as greater than 2 – 5 :1000, very high as greater than 5:1000).

All sexual partners of an individual diagnosed with HIV should be offered and recommended an HIV test

unless all episodes of sexual contact were known to be protected by Treatment as Prevention (i.e. the person living with HIV was on ART with a maintained undetectable viral load).

People with HIV should be provided options on how their partners can be contacted, as well as time to consider the best options, based on their needs (see also Point 14.17). People who do not want their partners to be contacted or need time to consider should be supported in their decision. Where feasible and acceptable to the client, provider-assisted referral should be prioritized, as it is highly effective and provides the opportunity to offer comprehensive prevention interventions to partners who are HIV-negative but remain vulnerable to HIV acquisition. Ensuring testing for all untested biological children of people who are HIV positive is required

All pregnant women in the UK are offered opt out HIV screening as part of their antenatal care. Uptake of HIV screening among women who attend for antenatal care is very high (>99%) and positivity remains low (0.013%).⁸²

Use of diagnostic tests in blood donor screening

Donor selection criteria aim to ensure that the population eligible to donate blood are at low risk for viral infections which have potential to be transmitted

via transfusion. Data confirm this to be an effective strategy, for example, the UK prevalence of HCV infection is 0.67% but the prevalence among first-time blood donors meeting donor selection criteria is 0.03%. Testing strategies employed to assess the suitability of donated blood for transfusion are therefore used in the context of very low chance of infection but, given that it is essential that all infections are detected, assays with high sensitivity are used.

Testing for HIV in donated blood was performed from the mid-1980s by screening for the presence of anti-HIV antibody. Advances in testing technologies led to the implementation of combined testing for anti-HIV antibody and HIV antigen in 2001, with NAT assays introduced in 2003. The UK Transfusion Guidelines⁸⁹ suggest the use of these combination HIV Ab/Ag serological assays because their use allows detection of the p24 antigen in samples which may not yet contain anti-HIV antibodies, thereby shortening the residual window period and reducing the risk that an infected donation may be missed. The UK requirement for the minimum level of sensitivity for the performance of HIV 1+2 serological screening is that a positive result should be obtained with the UK anti-HIV 1 working standard, which can be obtained from the National Institute for Biological Standards and Control (NIBSC). This standard must be included in each series of tests as a positive control, as well as any manufacturer's controls. These steps ensure validity

of test results. HIV Ab/Ag combination assays used by the blood services report sensitivity of 100% and specificity of >99.5%. Any samples from donations which are found to be reactive are then subject to confirmatory testing.

NAT assays are employed to identify the presence of HIV-RNA within a sample which may identify cases of early infection in which HIV Ag/Ab is not yet positive. There is no specific UK requirement for the minimum sensitivity of HIV NAT. However, a standard is available and all assays must be appropriately controlled. Samples from individual donations are pooled for initial testing. If a pool is reactive, the samples which make up the pool are tested individually to identify the reactive donation(s).

The signs and symptoms a person may experience when first infected with HIV (Point 14.6)

There is considerable variation in the symptoms and signs that a person may develop when they first acquire HIV – some people have no symptoms whilst others become extremely unwell.⁹⁰

The early stage of infection is taken as the first six months following viral acquisition. During this time, HIV undergoes very active replication and the level of virus in the body (the viral load) is very high, which makes this a period of elevated infectiousness.

People who are seen rapidly after HIV acquisition may present before they have detectable levels of routine diagnostic HIV-specific antibodies, which can make the diagnosis difficult.

The level of viral replication stabilises and reaches a steady state known as ‘the viral set point’ by approximately six months of infection. The viral set point can vary considerably between individuals and is correlated with the rate of progression of HIV disease, with a higher viral set point being linked to more rapid progression.

The stages of the development of laboratory markers of HIV and changes in viral load concentrations

during early HIV infection are classified by the Fiebig classification.⁹¹

The first two weeks immediately following infection are typically 'silent' without any symptoms or signs. Between two and four weeks following infection, a proportion of people will develop the symptoms and signs of 'acute' HIV infection (also known as 'primary HIV infection' or 'acute retroviral syndrome'), which was first described in 1985.⁹² Estimates of the proportion of people with early HIV infection who experience symptoms vary widely from fewer than 40% to more than 90%.^{93,94}

The 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, faint 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). In rare cases there may be signs of meningitis or of direct brain infection (encephalopathy). In most people, the illness lasts up to three weeks, resolves on its own and recovery is usually complete.

In some people, the syndrome may last longer or be more serious. Acute HIV infection can occasionally lead to profound immunosuppression due to the marked fall in the CD4 cell count, which in turn may make people susceptible to unusual or opportunistic

infections. Prolonged or more serious acute infection has been associated with poorer long-term prognosis.

Acute HIV infection is frequently undiagnosed or misdiagnosed as the non-specific nature of many of the symptoms and signs means that it may be confused with other viral infections such as Epstein Barr virus (glandular fever). Because symptoms are unspecific and variable, the diagnosis of HIV infection is rarely made without additional testing. Possible risks for HIV infection may not be routinely explored and symptoms may occur when antibodies to HIV may not yet have been produced. Laboratory tests to identify other viral components such as p24 antigen or HIV RNA may be positive before a sensitive HIV antibody test. If early or acute HIV infection is suspected but standard diagnostic tests are negative, then repeat testing seven days later is recommended.

The period of clinical latency (Point 14.7 and Supplementary Questions 8 and 21)

This section describes the period that may elapse between first acquiring HIV and symptoms of AIDS first emerging (a 'latency period') and what is known about any factors which may affect the length of this latency period either by shortening or prolonging it.

There is variation in the rate at which untreated HIV progresses. Following the early stage of infection, most people with HIV infection are asymptomatic for some years. This is known as 'clinical latency'. However, despite the absence of symptoms, the virus continues to actively replicate which results in ongoing CD4 cell destruction and progressive immune dysfunction. Without treatment, most people with HIV have a gradual decline in CD4 count over a period of approximately 8 to 10 years before the development of symptomatic disease, a CD4 count less than 200 cells/mm³ or to AIDS. Long-term HIV infection is associated with increased levels of inflammation and immune activation which contribute to both loss of CD4 cells and to elevated rates of number of non-communicable conditions amongst people with HIV.^{95,96}

A subgroup of people with otherwise asymptomatic infection may have persistently enlarged lymph nodes (persistent generalised lymphadenopathy, PGL). The

nodes are usually symmetrical, firm and non-tender. The spleen may also be enlarged. Similar disease progression has been noted in those with or without PGL. Nodes may disappear with disease progression.

In the absence of antiretroviral therapy, the factors that influence the period of clinical latency may be either pathogen or host related.

Viral factors: a higher viral set point and high baseline viral load are both associated with a faster rate of loss of CD4 cells and more rapid progression to symptomatic disease. The type and strain of HIV may be important, with evidence that the CD4 decline in HIV-2 is slower than in HIV 1 and the symptomatic period is longer. Differences in HIV 1 subtype have been implicated although the major geographical and social variables associated with differences in subtype complicate the picture. The type of cellular receptor that the virus uses to enter cells may be important with viruses that use the CXCR4 receptor leading to more rapid progression.

Host factors: CD8 lymphocytes are important in viral control – higher numbers and proportions of circulating CD8 lymphocytes are associated with reduced viral turnover and slower progression. People with cells that express the HLA -B57 marker have lower viral set points and slower disease progression. Older age has been associated with more rapid progression. Gender and pregnancy per se do not appear to have

a direct impact on the rate of HIV progression. High levels of alcohol consumption have been linked to CD4 count decline.

A small number of people with HIV known as 'long-term non-progressors' may continue with a CD4 count within the normal range over many years. Within this group, a sub-population of people ('elite controllers') maintain a viral load that is less than 2,000 copies/mL or even to undetectable levels without therapy. Elite suppression occurs in approximately 1 in 500 people with HIV. This is not permanent and over time elite controllers lose virologic and immune control with consequent disease progression.

The mechanisms of elite control remain incompletely understood. Potential factors include infection with types of HIV that are less able to replicate, the possibility that individuals may have innate resistance to HIV-1 infection, as well as genetic variations that can modify various aspects of the host immune response.⁹⁷

The presence of other infections such as tuberculosis, syphilis and parasitic worms has been associated with more rapid CD4 cell decline.

Hepatitis G (GBV-C) is caused by a small RNA virus with similarities to Hepatitis C Virus (HCV). There have been several reports associating GBV-C with a better outcome of HIV infection. In general, GBV-C/HIV co-infection is associated with lower HIV viral load, slower progression to AIDS and improved response

to HIV treatment. These effects are more likely to be seen with advanced HIV infection (low CD4 counts).⁹⁸ Theoretically, in HIV/HCV/GBV-C triple infected individuals, treatment of HCV with interferon could also lead to clearance of GBV-C which may, paradoxically, worsen outcome of HIV infection. However, this was not supported by clinical studies.

Complications of HIV and the development of AIDS (Point 14.9 and Supplementary Question 8)

The natural course of HIV – in the absence of antiretroviral therapy – is shown in Figure 2. In an era when effective treatment for HIV is consistently available, where people with HIV are diagnosed promptly and are able to access lifelong treatment, HIV has evolved from a universally fatal infection to a long-term manageable condition with a life expectancy that can match that of the general population. In these settings, the complications of HIV associated with immunosuppression have become much less common whilst other conditions, notably coinfections and conditions associated with low-grade inflammation and with ageing, are seen more frequently.⁹⁹

This response takes the natural history and complications of untreated HIV as its focus.

The complications of HIV infection

The spectrum of disorders associated with HIV infection is broad and the result of HIV-associated immune dysfunction, direct HIV effects and the drugs used to treat the condition, as well as coexisting conditions, including depression and anxiety and co-infections such as hepatitis. Health-related quality of

life is lower amongst people living with HIV than the general population.

The level of HIV RNA, which reaches extremely high values shortly after primary infection, usually decreases to less than 1% of the maximum value at the time of first HIV antibodies and remains relatively stable for a number of years. This level is called 'the viral set point'. The level of the viral set point determines the speed of disease progression. The higher the viral set point, the faster the decrease of CD4 T cells.

CD4 T cells usually drop considerably during acute primary infection. Subsequent CD4 counts recover after a few months to values within the normal range, though pre-infection values are rarely reached. During the progressive course of HIV infection, a gradual decrease of CD4 T cells is observed.

Without treatment, over time as the viral load rises and the CD4 count falls, the immune system becomes increasingly dysfunctional and an array of problems can develop. These can include non-specific symptoms such as fatigue, weight loss and sweats, particularly at night, and conditions classified according to the CDC as Category B may develop (Table 1, please see also Figure 2.5 in the Krever report, Chapter 2).¹⁶⁴ Among these, oral thrush, oral hairy leukoplakia and herpes zoster are particularly noteworthy, and HIV infection as an underlying

diagnosis should always be taken into account. Conditions in Category B are not AIDS-defining. However, their occurrence is defined as symptomatic of HIV infection and suggests a disturbed cellular immune system.

With further immunosuppression, the person is susceptible to an increasing range of opportunistic infections and tumours, which meet the criteria for the diagnosis of AIDS (see CDC Category C classification list in Table 1).

While most patients with less than 1,000 HIV RNA copies/ml are usually not affected by AIDS even 12 years after primary infection, more than 80% of patients have developed AIDS only two years after infection if the viral load remains at levels above 100,000 copies/ml.¹⁰⁰ The risk for AIDS-defining illnesses increases with time when CD4 T cells decrease below 200. In the pre-ART era, the average time between the first manifestations of AIDS and death was two to four years.

Apart from the level of HIV RNA and CD4 T cell count, the age of the patient is another important risk factor for progression to AIDS. The increasing risk with age has been described to be similar in haemophiliacs and homosexual men.¹⁰¹ Regarding AIDS-defining events, some differences exist between different affected key populations. For example, Kaposi sarcoma is rarely found in haemophiliacs and mostly found in

homosexual men. Table 1, Categories B and C, lists a number of health complications.

There are, however, a number of health complications listed which can also be observed independent of HIV. The question mostly is whether the medical condition occurred prior to or after HIV infection had taken place. For example, epilepsy can develop independent of HIV but can also be a sequelae of cerebral toxoplasmosis which is an AIDS-defining event.

With early intervention of effective ART, the majority of people with HIV in resource-rich settings begin treatment whilst asymptomatic, before the onset of significant immunosuppression. Progression to an AIDS-defining event is now uncommon.

In an individual person, the consequences of HIV-related immune dysfunction depend on at least three key factors:

- **The microbial exposure of the person throughout life.** Many clinical complications are the result of reactivation of a previously acquired infection, which has been held in a latent state by the immune system. Geographical factors can influence the microbial repertoire of an individual person. Organisms requiring effective cell-mediated immunity for their control are most likely to cause problems.
- **The pathogenicity of organisms encountered.** High-grade pathogens, such as *Mycobacterium*

tuberculosis, Candida and the herpes viruses, are able to cause clinical problems even when immunosuppression is mild, and so are likely to occur earlier in the course of HIV infection. Less virulent organisms become problematic as immunodeficiency becomes more profound.

- **The degree of immunosuppression of the host.** When patients are severely immunocompromised (CD4 count <100 cells/mm³), disseminated infections with organisms of very low virulence, such as *M. avium-intracellulare* (MAI) and *Cryptosporidium*, can establish themselves. These infections are very resistant to treatment, mainly because there is no functioning immune response to clear organisms.

HIV can also directly infect cells of the nervous system, skin, gut and kidneys which if untreated can cause direct organ damage. Examples include AIDS Dementia Complex, HIV-associated nephropathy (HIVAN) and dry, itchy skin.

HIV is related to abnormalities in the inflammatory response which are implicated in higher rates of allergic reactions and some autoimmune conditions (for example, psoriasis). HIV-associated inflammatory responses are also linked to the development of neurological, renal, cardiovascular and bone disorders which are more prevalent amongst people living with HIV. Even with effective antiretroviral treatment, people with HIV have higher levels of multimorbidity

occurring at younger age than those who are HIV negative. Frailty and its associated disabilities appear to occur at a younger age in people with HIV. Leading causes of hospital admission of people with HIV in Europe in 2017 included respiratory illness, psychiatric conditions, and cardiovascular, renal and neurological disorders. Data from the UK show 75% of those living with HIV have at least one other long-term condition including mental health conditions, hypertension, lipid disorders and diabetes. Identification of comorbidities, their risk factors and interventions for prevention through an integrated, outcomes-focused person-centred approach is central to HIV care (see Point 14.13).

People who start ART when profoundly immunosuppressed may experience inflammatory symptoms associated with the recovery of their immune system, known as ‘immune reconstitution inflammatory syndrome (IRIS)’. Symptoms of existing infections may worsen, or symptoms of undiagnosed conditions may emerge (see also Point 14.12).

Indicator conditions

Ensuring that the diagnosis of HIV is made promptly is very important in securing best outcomes.

Recognising the conditions, symptoms and signs that are associated with HIV in people who are not yet diagnosed, and recommending HIV testing is critically important in reducing rates of late and undiagnosed

HIV. Anyone presenting to any clinical service with any of the stage 3/AIDS-defining conditions should be immediately tested for HIV. Other conditions in which the prevalence of undiagnosed HIV is more than 0.1%, and where an HIV test is indicated, include sexually transmitted infections, malignant lymphoma, herpes zoster, hepatitis B or C (acute or chronic), unexplained lymphadenopathy, mononucleosis-like illness, community-acquired pneumonia, unexplained leukocytopenia/thrombocytopenia lasting more than four weeks and seborrheic dermatitis/exanthema.¹⁰²

Monitoring of the viral load and CD4 count

The CD4 count

Lymphocytes are white blood cells of which T lymphocytes are one type. Types of lymphocytes can be distinguished by their molecular markers which are known as 'cluster determinants'. T lymphocytes that 'help' other parts of the immune system carry cluster determinant 4 and are known as CD4+ T helper lymphocytes. It is these cells that are both targeted by and gradually become depleted by HIV over time. These cells are responsible for the co-ordination of the immune response to infection and for immunological memory. Both the absolute CD4 count and its percentage of total lymphocytes fall as HIV progresses. In a person with a healthy immune system, the CD4 count range in blood is between 500 and 1,500 cells/mm³. As the immune system becomes

progressively more damaged by HIV infection, the CD4 count falls and the risk of complications of HIV increases, with the greatest risks occurring at counts below 200 cells/mm³. Up until 2015, CD4 counts played an important part in decision making for when to start antiretroviral therapy – today, however, patients are recommended to start ART irrespective of CD4 count. The CD4 count remains important for assessing stage of disease and determining interventions such as prophylaxis against opportunistic infections and malignancy and the safety of live vaccines.

Monitoring in the UK follows the British HIV Association Guidance.¹⁰³ The baseline CD4+ T cell count and percentage should be measured at first presentation for clinical staging and to assess the absolute urgency to start ART. As per current treatment guidelines, most patients now start treatment within a few weeks of HIV diagnosis, many within a few days. For those presenting with more advanced disease (as determined by CD4+ count) or certain AIDS-defining conditions, the urgency to start treatment is higher. On treatment, the CD4 count is monitored every three to six months for those patients with advanced disease. However, once virologically stable on ART and with a CD4 consistently above 350cell/mm³, routine monitoring of CD4 counts is no longer recommended.

The significance of the CD4 count for the person with HIV is as a marker of the level of immunosuppression,

the relative risk of complications developing and, until recently, a guide to when to start and/or the urgency of starting ART. It is also useful for making decisions on other preventative interventions including vaccinations.

The viral load

The amount of HIV RNA measured in the circulation of a person with HIV is known as 'the HIV viral load'. The viral load is highest in primary HIV infection but by about six months after acquisition it has stabilised to a 'set point'. Higher viral loads are linked to more rapid loss of CD4 cells and are co-related with infectiousness. The viral load level immediately prior to starting ART influences the choice of agents used in ART, in that several treatments have reduced efficacy at a viral load >100,000 copies/ml and are best avoided if the viral load is higher.¹⁰⁴ The viral load is the standard marker of antiretroviral treatment efficacy. Effective antiretroviral therapy suppresses viral activity and the viral load falls to a level where assays cannot detect RNA, usually four to six months after starting ART. This is referred to as an undetectable viral load and the aim of ART is securing this level of viral suppression for the long term. Although there is generally a good correlation in the measurements between different manufacturers' assays, their lower limit of quantitation differs (range 20–75 copies/ml). A viral load below 50 copies/ml is generally considered to be 'undetectable'.

BHIVA guidelines¹⁰³ recommend that viral load is measured at time of diagnosis and then at intervals of four to six months if ART is not started. Following the initiation of ART or changes in therapy, a reduction in viral load should be seen by four weeks, falling to lower levels by 10–12 weeks, when repeat viral load testing should be carried out, before becoming undetectable at four to six months. Once undetectable and the patient is virologically stable on ART, viral load is routinely monitored every six months. People with HIV whose viral load is consistently undetectable on ART are not able to pass HIV to their sexual partners and vertical transmission is prevented.^{105,106}

Even with excellent adherence, occasionally the viral load can transiently become detectable at very low levels only to revert to undetectable again. This is referred to as a 'blip'. However, a viral load that is consistently detectable and/or rising to above 200 copies/ml indicates virological failure. The patient should be assessed for adherence and may need to switch therapy.

The significance of the viral load for the person with HIV is as a marker of the level of activity of their HIV infection, a guide to the appropriate antiretroviral drug regimen, a marker of the effectiveness of their ART and an indicator of the need to switch treatment. Once the viral load is consistently undetectable, the person with HIV is no longer able to pass on HIV to other people (Undetectable = Untransmissible, U=U)^{107,108}

which is of major significance for the lives and the social, sexual and reproductive choices for people living with HIV and their partners.

A review of the associated illnesses that HIV and/or AIDS (or treatment for HIV and/or AIDS) can cause to those infected (Point 14.13)

The natural course of HIV – in the absence of antiretroviral therapy – is shown in Figure 2. Shortly after infection, an acute/primary infection syndrome is observed in some patients. This syndrome is characterized mainly by lymphadenopathy, fever, maculopapular rash and myalgia and usually does not last longer than four weeks (see Point 14.6 for more information).

The symptoms are unspecific and variable so that the diagnosis of HIV infection is rarely made without additional testing. A period of several years follows when most patients are clinically asymptomatic.

Thereafter, symptoms or diseases may occur, classified according to the Centers for Disease Control and Prevention (CDC) as Category B (Table 1; please see also Figure 2.5 in the Krever report, Chapter 2).¹⁶⁴ Among these, oral thrush, oral hairy leukoplakia and herpes zoster are particularly noteworthy, and HIV infection as an underlying diagnosis should always be taken into account. Diseases of category B are not AIDS defining. However, their occurrence is defined as symptomatic of HIV infection and suggests a disturbed cellular immune system.

Later in the course of HIV infection, AIDS-defining illnesses occur at a median of 8–10 years after infection. Without highly active antiretroviral therapy, these illnesses eventually lead to death after a variable period of time.

The level of HIV RNA, which reaches extremely high values shortly after primary infection, usually decreases to less than 1% of the maximum value at appearance of HIV antibodies and remains relatively stable for a number of years. This level is called 'the viral set point'. The level of the viral set point determines the speed of disease progression. While most patients with less than 1,000 HIV RNA copies/ml are usually not affected by AIDS even 12 years after primary infection, more than 80% of patients have developed AIDS only 2 years after infection if the viral load remains at levels above 100,000 copies/ml.¹⁰⁰ The higher the viral set point, the faster the decrease of CD4 T cells. CD4 T cells usually drop considerably during acute primary infection. Subsequent CD4 counts recover after a few months to values within the normal range, though pre-infection values are rarely reached. During the progressive course of HIV infection, a gradual decrease of CD4 T cells is observed. The risk for AIDS-defining illnesses increases with time when CD4 T cells decrease below 200. In the pre-ART era, the average time between the first manifestations of AIDS and death was two to four years. Apart from the level of HIV RNA and

CD4 T cell count, the age of the patient is another important risk factor for progression to AIDS. The increasing risk with age has been described to be similar in haemophiliacs and homosexual men.¹⁰¹ With regard to AIDS-defining events, some differences exist between different affected key populations. For example, Kaposi sarcoma are hardly found in haemophiliacs and mostly found in homosexual men. Of the listed health complications many can be found in Table 1 under Category B or C. There are, however, a number of health complications listed which can also be observed independent of HIV. Most significant is whether the medical condition occurred prior to or after HIV infection. For example, epilepsy can develop independent of HIV but also can be a sequela of cerebral toxoplasmosis which is an AIDS-defining event.

Similarly, kidney stones can occur independent of HIV but can also be a side effect of antiretrovirals such as atazanavir, darunavir or indinavir. Gallstones are not HIV related.

It is important to highlight that, due to the transmission pathways for people with inherited bleeding disorders, HIV infections mostly occurred in the 1970s and 1980s and, as such, many individuals were exposed to first generation antiretrovirals which were associated with significantly more toxicity than subsequent regimens which involved some of the more recent drug classes. Within the NRTI (first drug class available) drug class

mitochondrial toxicity was prominent including risk for development of lipoatrophy, anemia, pancreatitis, diabetes, polyneuropathy, myopathy and hepatic steatosis. Among the protease inhibitor first generation drug class gastrointestinal toxicity, kidney stones (indinavir), diabetes (indinavir) and dyslipidemia were the most common adverse events. For NNRTI it was drug rashes, hepatotoxicity and CNS-toxicity.

The mental health of people living with HIV is less good than that of the general population. Depression and anxiety are amongst the major disorders reported. Poor mental health has been linked to HIV-associated stigma.

With effective ART, people with HIV are living longer and are developing the disorders associated with older age. These conditions, including cardiovascular disease, hypertension, renal disorders, bone pathology and neurocognitive problems are more common and occur at an earlier age in people with HIV than the general population. There is a clustering effect, leading to multiple conditions occurring together (multimorbidity). This has a direct impact on the quality of life of people living with HIV and can lead to complications associated with multiple medications, co-ordination of care and quality of life.¹⁰⁹

A description of the symptoms – physical, mental, and cognitive – a person may experience as HIV progresses (Point 14.8)

The way that an individual experiences the effects of HIV will differ depending on their particular circumstances, the stage at which the infection is diagnosed, co-existing conditions and the treatment interventions that are being made. Demographic, cultural and social factors will all influence the impact that HIV may have on an individual and their response.

HIV-associated stigma may prevent people from accessing the care and support that could make a difference, may lead to discrimination and self-stigma which can undermine people's self-esteem and self-worth, and can have a negative impact on mental health.

Today in the UK, HIV disproportionately affects communities in which people may already be underserved and/or marginalised, and the intersectionality of characteristics including gender, ethnicity, migration status, sexual orientation and substance use with HIV infection frequently creates a particularly difficult environment. The focus of the Inquiry is on those people who have acquired HIV from infected blood and blood products. It is important to recognise that, although there are commonalities

amongst people who experience HIV infection, there is also considerable variation regarding the significance of various social and psychological impacts.

HIV testing

Today national guidelines on HIV testing advocate expanded HIV testing across healthcare settings, with the aim of benefiting both individual and public health. In the past, before the availability of effective treatment and in an environment of stigma, misconception, fear and discrimination, extensive consideration with a trained healthcare professional was recommended prior to undertaking the HIV test: 'pre-test counselling'. The focus of pre-test counselling was to individualise the implication of receiving a HIV positive result where, prior to treatment, there were few benefits to knowing the result and many challenging consequences of such a diagnosis. When the test result was received, further support and counselling were given. For those with a negative result, the focus of the discussion was on reducing activity that could increase the risk of HIV acquisition. If the result was positive, the post-test counselling session was an opportunity to offer support, assist with adjustment and establish appropriate referrals for ongoing care and management. Today, lengthy pre-test counselling is no longer recommended prior to testing. Guidelines are provided by The British HIV Association (BHIVA) to enable any clinician to perform an HIV test within good

clinical practice and to encourage ‘normalisation’ of HIV testing and rapid referral to specialist services.

There were many in the 1980s, when HIV testing first became available, who were part of cohorts considered at high risk of having acquired HIV and were already established patients within the health service – particularly those with haemophilia who had received factor products and intravenous drug users. Blood was tested, sometimes on stored samples, and patient consent not obtained. The benefits offered by pre- and post-test counselling in such circumstances would have been absent.

For further details on HIV testing procedures, see Point 14.17. For details on diagnostic tests, see Point 14.4.

Experience of HIV infection

Today, people diagnosed HIV positive in the UK will be referred rapidly into specialised services with the option of immediate effective treatments, care and support. Patients, partners and family members should receive information and support as required (see Point 14.17). Further clinical assessment and investigations will determine appropriate treatment options for consideration, and ongoing physical and mental health monitoring will be established. Discussions with experienced healthcare workers will assist patients with decisions related to disclosure of their HIV diagnosis to family, friends, workplaces, prevention

of transmission to sexual partners or mother-to-child transmission, contraceptive and conception advice.

With effective treatments, the impact of HIV infection today is different from the pre-ART era, with significantly fewer HIV-associated physical symptoms and illness. Increasing social awareness and protective public policy has helped to change attitudes and reduce discrimination towards those living with HIV. However, many people have experienced and continue to experience social and psychological challenges as well as dealing with stigma. Both external stigma and self-stigma remain a major complication of HIV.

Social and psychological impact of HIV infection

All long-term conditions have psychological impacts, both on those with the condition and those who are close to them. Ill health affects an individual's emotional state and their self-identity and may require major adjustments – for example, to accommodate pain, incapacity, long-term drug treatment and side effects, clinical interventions and changes to lifestyle. For some, such adjustments may be straightforward with personal and professional support; others may experience what is considered an adjustment disorder or stress response syndrome. Such a response can manifest as tearfulness, feelings of hopelessness, loss of motivation, and interest in work or normal life activities. Professional support at HIV diagnosis and

consistently during ongoing care and management is required to prevent or offer continued support.

The extent of social disruption and hardship experienced by those with HIV infection is influenced by an individual's social circumstances, age, life stage, economic situation and social support.

Today, with a life expectancy near to the same as the general population, HIV for many people has a different level of social psychological impact from that prior to effective treatment in the 1980s and 1990s when life expectancy was uncertain and prognosis poor. For younger people, school and educational attainment and achievement may have been negatively affected. HIV-related health issues had a direct impact on employment and career opportunities, because of absence from work due to ill health or due to stigmatising workplaces reducing employment opportunities. Challenge to employment resulted in financial hardship often borne by partners. HIV had an impact on travel due to ill health or because of visa restrictions. Property was unattainable because mortgages and health insurance were restricted. Friends, family members and social groups may have failed to offer the support expected. Within families and relationships, HIV could have a profound affect; sexual transmission or fears of sexual transmission could break up relationships and have an impact on new relationships. Fears of transmission to a baby could result in terminations of pregnancy and choices

to not have children. Parenting was affected by HIV-related ill health: children caring for a sick parent, or parents caring for a sick child. Grief is more difficult and bereavement more profound when cause of death cannot be named and shared openly.

HIV is a medical condition that carries considerable, specific stigma, often because people lack information or they make moral judgements about how someone has contracted HIV. Stigma was attached to a misunderstood fear of casual transmission, but more by the concentration of HIV among those in society already stigmatised: gay men, sex workers, intravenous drug users. Stigma was fuelled by negative media coverage and resulted in people with HIV experiencing hostility, physical and/or verbal abuse, avoidance and exclusion. Although not as widespread, stigma and discrimination continue to have a detrimental impact on the lives of many people with HIV infection.

In a setting of stigma and discrimination, patients faced many challenging social and psychological issues. Before effective ART in the late 1990s, such challenges were dealt with alongside ongoing and deteriorating health problems.

Physical impact of HIV infection

Initial HIV infection may manifest as a seroconversion illness, usually a mild to severe flu-like condition (further details in Points 14.6, 14.13). The virus at this

stage is rapidly replicating and infectivity is very high. Antibodies may not yet be present and the HIV test may be negative. This phase of the disease usually lasts for 2 to 4, but up to 12, weeks. This stage of HIV infection may pass unnoticed, especially if not associated with an awareness of infection risk. Individual HIV testing and a positive diagnosis may occur long after this phase of acute infection. Today with effective ARV treatment available at diagnosis, guidelines encourage HIV testing in all healthcare settings in order to reduce the proportion of individuals with such undiagnosed HIV infection.

In the presence of untreated HIV infection, the virus replicates within the CD4-carrying cells of the immune system – the T4 lymphocytes. The immune system is rendered increasingly weakened and becomes vulnerable to multiple opportunistic infections (OIs) – bacterial, fungal, viral and cancers. These organisms are present in the human body but become pathogenic in the presence of a weakened immune system.

Symptoms may develop during the ‘latent’ phase of HIV infection (CDC classification B) and may relate either to dysfunctional immune regulation or progressing immune deficiency. People with HIV infection may experience persistently swollen lymph nodes (persistent generalised lymphadenopathy/ PGL) and unpleasant skin complaints. As the immune system declines, the initial symptoms of HIV infection represent the body’s poor response to infections such

as candida (thrush) or tuberculosis. In this situation, people with HIV infection may experience recurrent viral infections such as herpes and warts. Shingles may be the first indication that the immune system is impaired. Common bacterial pathogens frequently occur causing respiratory symptoms – difficulty breathing, cough, fevers, sweats – and gastrointestinal symptoms such as stomach cramps, diarrhoea and poor appetite. Such clinical features and symptoms – oral candidiasis (thrush), oral hairy leucoplakia and general symptoms such as fever, weight loss, fatigue, night sweats, and diarrhoea – predict the progression to AIDS. This phase was formerly called ‘AIDS-related complex’, or ‘ARC’.

Symptoms experienced as HIV infection progresses – AIDS

Prior to effective treatment and prophylaxis (preventative treatment) for opportunistic infections, pneumocystis carinii pneumonia (PCP) was the most common first AIDS-defining illness (with more advanced knowledge in 1999, the condition was renamed ‘pneumocystis jiroveci’). Many people with HIV infection died as a result of PCP, which typically presented when the CD4 count reached around 200 cells/mm³. As effective treatment and prophylaxis for PCP was introduced, patients survived PCP but progressed to experience other opportunistic infections which appeared when the immune system became

further weakened. Patients were living longer but facing more frequent and multiple debilitating illnesses. For as long as the immune system continued to deteriorate, death was inevitable.

In 1986, the Centers for Disease Control and Prevention (CDC) classified AIDS as the presence of one of 23 clinical conditions. The classification was revised in 1993¹¹ to emphasise the clinical importance of a CD4 T-lymphocyte count. An AIDS definition included all people with less than 200 CD4+ T-lymphocytes/uL. Three clinical conditions were added to the definition of AIDS in 1993: pulmonary tuberculosis, recurrent pneumonia and invasive cervical cancer.

Table 2: The symptoms caused by some of the major HIV-associated pathogens.

Candidiasis of oesophagus, bronchi, trachea, or lungs – commonly known as thrush	A yeast infection causing pain, difficulty in swallowing and loss of appetite.
Cryptococcal infection: a fungal infection. Most commonly causes meningitis	Headaches, nausea, fever, fatigue, altered mental status, irritability and seizures.
Cryptosporidiosis: a parasite in the gut	Causes chronic diarrhea with frequent watery stools, stomach cramps, nausea, fatigue, weight loss, appetite loss, vomiting, dehydration and electrolyte imbalance.

Cytomegalovirus (CMV)	<p>Eye infection: retinitis, causing blurry vision, loss of central vision and blindness.</p> <p>Gut infection: colitis, fevers, diarrhea and stomach pain.</p> <p>Oesophagitis: oesophageal ulcerations, severe pain and difficulty in swallowing.</p> <p>Lung infection: Pneumonitis pneumonia-like symptoms.</p>
Encephalitis infection of the brain	Confusion, fever and tiredness. HIV encephalopathy is a direct result of HIV on the brain and has similar symptoms.
Herpes simplex	Recurrent very painful skin and mucous membrane. Ulceration can also cause bronchitis, pneumonitis, or esophagitis.
Histoplasmosis: fungal infection	Can cause pneumonia or disseminated infection. Leads to fever, fatigue, weight loss, difficulty in breathing, swollen lymph nodes and pneumonia-like symptoms.
Kaposi's sarcoma (KS): a rare type of cancer of the lymph and blood vessels	Red or dark purple lesions under the skin and living of mouth, nose, throat and other internal organs. Most common in people who acquired HIV sexually.
Lymphoma	Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL), primary central nervous system (CNS) lymphoma of brain.
Mycobacterium avium intracellulare / complex (MAI/ MAC): bacterial infection that occurs with very advanced immunosuppression	Often disseminated infection. persistent fever, night sweats, fatigue, weight loss, anaemia, abdominal pain, dizziness, diarrhea and weakness.

Mycobacterium tuberculosis: bacteria that causes tuberculosis	TB can cause disease when there is only minimal immunosuppression and thus often appears early in the course of HIV infection. Occurs in the lungs and other body areas – malaise, night sweats, cough, fever, shortness of breath and weight loss.
Pneumocystis jiroveci infection. (previously <i>Pneumocystis carinii</i>). Most commonly seen as a lung infection	Often insidious onset over a period of weeks, with a prolonged period of increasing shortness of breath (usually on exertion), non-productive cough, fever and malaise, weight loss, night sweats and fatigue.
Progressive multifocal leukoencephalopathy (PML) caused by Polyomavirus infection. Viral infection of the brain	A progressive neurological and/or intellectual impairment, often including weakness or difficulties with speech, loss of coordination, difficulty walking, facial drooping, loss of vision, personality changes, difficulty speaking, muscle weakness. Usually inexorably progressive.
Salmonella	Recurrent bacterial infection from contaminated water and food – stomach cramps, bloody stools, diarrhoea, fever, headache, muscle pains, nausea.
Toxoplasmosis: parasitic infection usually of the brain	Causes multiple abscesses in the brain leading to altered mental state, confusion, delusional behaviour, severe headaches, fever, seizures and coma. Can affect eyes – pain and reduced vision.
Wasting syndrome	Cachexia, caused by HIV itself – progressive weight loss (>10%) weakness, fever, nutritional deficiency and diarrhoea.

Multiple medications were used for the many opportunistic infections both to try to prevent them and as treatment as they appeared. However, until specific treatments were developed to prevent HIV replication and maintain the immune system, death from AIDS was almost inevitable. Most emerging treatments, particularly the early antiviral treatments, had unavoidable, often intolerable, side effects which required further medication to limit side effects and sustain treatment options. Multiple tablets and medications would need to be taken several times a day.

This appalling combination of frequent bouts of severe ill health, often different concurrent illnesses and ongoing treatments with many intolerable side effects that required additional medications, had an enormous effect on patients' mental health and impact on everyday life – at school or work, social life and relationships with friends, families and partners – and often caused disconnection, isolation, anger, fear, anxiety and depression.

It is often difficult to distinguish between the symptoms of the multitude of possible opportunistic infections, the symptoms which relate to treatment side effects, the symptoms resulting from the direct effect of HIV (for example, on the gastrointestinal system and on the brain) and the symptoms associated with severe psychological and mental health.

Research and treatment and related medical monitoring for HIV conditions progressed rapidly from the early 1980s until by 1996 effective treatment became available in the form of 'HAART' (highly active antiretroviral treatment). The symptoms associated with HIV progression changed as treatment and prophylaxis for opportunistic infections improved, and as research and development of effective and more tolerable antiretrovirals against HIV became increasingly available. Physical illnesses decreased and side effects were progressively better managed. For those who had not died of AIDS, there was a new sense of hope and less focus on inevitable death. However, 15 years living with HIV-related illnesses and treatments, and a belief of inevitable death, had left many with compromised health, low educational attainments, poor work and career progression, psychological and mental health issues, and low finances – all of which had to be reviewed in light of a future living rather than dying.

Before the introduction of effective therapy, HIV was a progressive, universally fatal infection. The development of HAART has transformed the clinical outcomes for people living with HIV, extending life expectancy towards that of the general population, reducing ill health and preventing HIV transmission. Today the aim is to maximise wellbeing and keep people in good health by diagnosing HIV promptly, starting treatment before symptoms or ill

health develop, and preventing and treating other conditions associated with HIV. Today in the UK, symptomatic infection and opportunistic conditions in immunosuppressed patients are most commonly seen where ART is not available, or in people who are diagnosed late and have advanced infection.

There is still no cure for HIV and people live with a chronic, potentially infectious, stigmatising and sometimes unpredictable condition requiring daily medication for its control. Even with complete viral suppression, ART does not fully restore health, and treated infection is associated with a variety of complications and comorbidities, and non-AIDS complications, including cardiovascular disease, some cancers and impaired mental health. Measures of health-related quality of life are consistently lower amongst people living with HIV than in the general population.^{11,110,111}

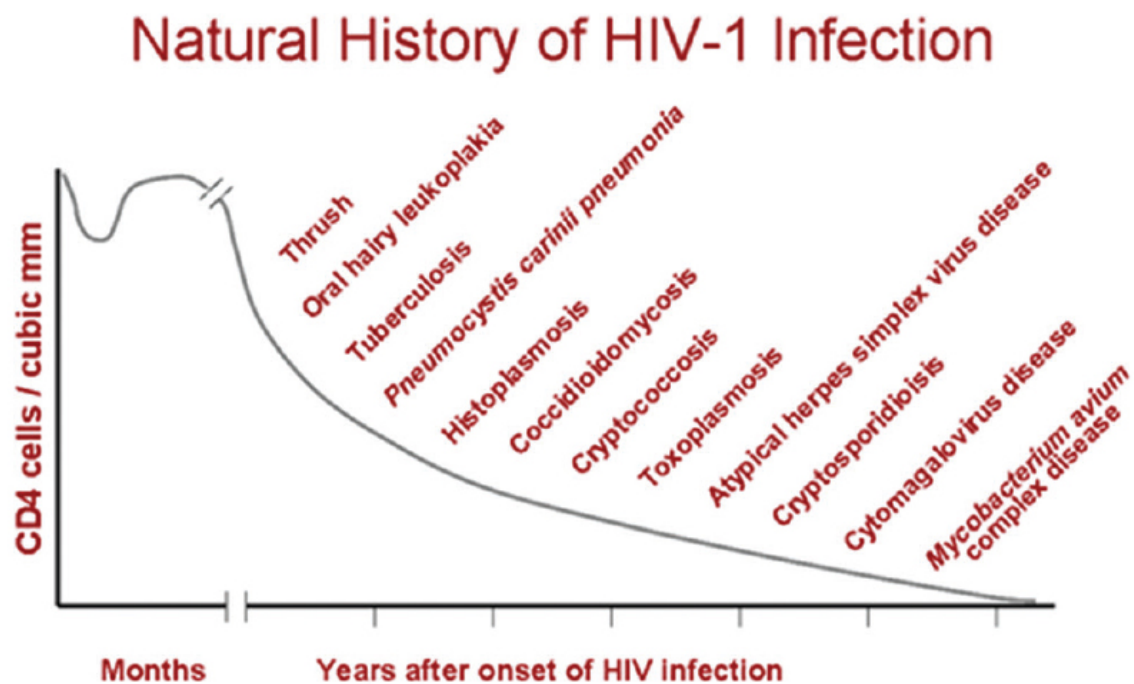


Figure 6: Opportunistic infections associated with advanced human immunodeficiency virus disease

Source: Microbiology Book, *Natural History of HIV-1 Infection*, accessed 28 January 2020, available at <<http://www.microbiologybook.org/lecture/images/natural-history.gif>>.

To what extent, and how, does HIV affect babies and children differently from adults? (Supplementary Question 22)

From the perspectives of the IBI, there are two major issues to consider. The first is the natural history of HIV drawn from publications in the early 1990s prior to effective combination antiretroviral therapy (ART). The second is to understand the major issues that are specifically relevant to young people growing up

with HIV during decades of gradual improvement in available treatment.

Natural history

Infants and very young children lack the full repertoire of mature immune responses that in adults can bring HIV replication under control following infection. Longitudinal studies of infants infected around the time of birth ('perinatally') demonstrated that HIV peaks in the circulation at very high levels (many millions of copies of HIV per ml of blood). The mature adult immune system typically brings the initial peak under control within three months, reducing the amount of HIV to below 100,000 c/ml, and frequently down to less than 10,000 c/ml. In contrast, young children were found to have a median (one measurement of average) of 100,000 c/ml two years after becoming infected perinatally.

The result of this impaired immune control, in the era before effective ART, was more rapid disease progression than in adult cohorts. Survival rates varied dramatically according to geography. In European and North American cohorts, 15% of perinatally infected children had died by age six years. In sub-Saharan African settings, only 15% were still alive at four years of age.

In all settings, about one fifth of the children had rapid disease progression, succumbing to pneumocystis pneumonia and other opportunistic infections within a

few months of birth. Impaired growth and development were common features. HIV can penetrate and cause damage in the brain, with lifelong consequences if the damage occurs as the brain is rapidly growing, particularly in the first two years of life.

Even in high-income settings, children with perinatally acquired untreated HIV rarely developed cancers because they died of other causes – predominantly infections. If the cellular immune system was damaged at the time children first met common childhood infections such as chicken pox, the infection could disseminate and involve internal organs including the lungs and liver, resulting in death. This was in contrast to adults with HIV infection who would have had such infections in childhood and would have some degree of pre-existing immunity when exposed in later life.

In about one fifth of the children, a lung condition rarely described in adults, called ‘lymphocytic interstitial pneumonitis’, caused inflammatory changes throughout the lungs. Sometimes this was sufficiently severe to limit exercise tolerance and require treatment with corticosteroids (with attendant adverse effects). A more common problem was the association with chronic lung disease due to damage to the small airways (bronchiectasis). Such children would have very frequent bacterial chest infections, persistent productive cough, debility and increased risk of fatal bloodstream infections.

There are sparse data describing the natural history of HIV acquired at different ages during childhood beyond the perinatal period. It is known that the CD4 counts, which are naturally much higher in infancy, decline to around adult levels by age five years. Broadly, acquisition of HIV between 5 and 15 years of age was associated with better survival than acquisition in later life in haemophiliac populations, due to the co-morbidities of older people especially when co-infected with HBV or HCV. It can be construed that survival improves if HIV is acquired after infancy, as the cellular immune system matures, but detailed survival data have not been published.

Growing up with HIV infection: specific issues for children and adolescents

As with adults, ART completely rewrote the natural history of HIV infection in terms of survival and quality of life for children with HIV infection. However, a fundamental difference for children throughout the early decades of the HIV epidemic was the lack of suitable antiretroviral drug formulations and dosing information. With the exception of didanosine, every ART drug was licensed for use in children years after licences for adults were granted. Younger children in particular were disadvantaged: efavirenz, for example, was never formulated for children age younger than three years despite being the first-line drug of choice for many years in adults. Most protease inhibitors

required boosting with ritonavir that, as a suspension, tasted truly unpleasant. These issues did nothing to help long-term adherence: persuading children to take medicines was a daily, distressing battleground for many parents and caregivers.

Strategic clinical trials tended to follow adult trials so that progression from mono- to dual- to triple-ART as standard of care for children lagged a year or two behind that of adults. Options for second- and third-line treatments were limited, resulting in children staying on their first-line treatment longer. This, and the problems of poor adherence, resulted in the selection of high-level, multi-class resistance, especially in the cohort who started treatment in the early 1990s. Most young people who initiated HIV treatment after 1998 will have been started on triple ART, with much lower rates of acquisition of drug-resistant HIV.

For a graphic illustration of all the issues that young people have faced, the 12-minute film created by the Children's HIV Association using statements drawn directly from their experience is recommended: 'Life growing up'.¹¹²

Stigma, both overt and internalised, has been experienced by the majority of young people growing up with HIV. For their caregivers, the fear of causing distress led to well-meaning but misguided delays in letting many young people know that they were living with HIV. Discovering that you had a potentially

sexually transmissible infection at the same time as going through adolescence and beginning to navigate towards first intimate relationships was devastating for many young people, leading to poor adjustment, immense anger and low self-esteem. In the past 20 years, healthcare professionals have been better at ensuring young people know the name of the virus ahead of entering puberty, typically by 11 years of age, but those infected in the 1980s and 1990s often found out in their mid-teens.

The long-term outcomes for young people surviving into adulthood are obviously not yet known. The survival estimates for people acquiring HIV mono-infection in adulthood have been published.¹¹³ Based on data from 18 European and North American cohorts comprising 88,504 patients initiating treatment between 1996 and 2010, a 20-year-old starting ART in the last of these time periods with a CD4 count above 350 was estimated to live to be 78 years. Given that young people infected during childhood would have been living with HIV for up to 20 years longer, it is a near-certainty that their life expectancy would be less than 78 years and possibly up to 20 years shorter. However, these crude estimates do not take into account advances in HIV therapy and other more broad medical interventions that will influence survival.

Data from the national UK/Ireland paediatric HIV cohort (CHIPS) were presented at the 10th International Workshop on HIV Pediatrics, Amsterdam,

July 2018. Asad et al.^{114,115} reported that, of 474 young people with perinatally acquired HIV who transitioned at a median age of 18 years, 14 (3%) died, 36% experienced severe immunosuppression (CD4 <200 cells/mm³) and 46% experienced viral rebound (viral load >400 copies/ml on two consecutive samples) by six years into adult care. Of 387 with more complete clinical data, 27 (7%) had developed a new AIDS event at a median follow-up of 3.3 years. The cumulative incidence of mortality or a new AIDS event was 11% by six years.

In a smaller cohort from Imperial College Healthcare NHS Trust, London, UK, Foster et al. have reported that, of 180 young people with 921 person years of follow-up post transition, the all-cause mortality rate was 10-fold higher than in the age-matched general population. Seventeen (9%) developed a new AIDS-defining diagnosis, 20% had experienced anxiety and/or depression, 3 had attempted suicide and a further 4 had self-harmed.¹¹⁶

From the same cohort, extended to include 10–24-year-olds with perinatally acquired HIV, Chhabra et al. reported that 8/290 (2.8%) developed a malignancy. This represents a 13% higher incidence compared to the age-matched general population.¹¹⁷

Several studies have identified biomarkers and other measurements that predict a higher risk of cardiovascular disease in adolescents and young

people with perinatally acquired HIV, although none have expressed the data as a quotable percentage risk of heart attacks or stroke. For example, the PositHIVe Health Study compared a cohort of 65 Brazilian children with HIV aged 8–15 years with 65 age- and sex-matched HIV-negative controls.¹¹⁸ The young people with HIV infection had higher inflammatory markers in their blood, higher levels of atherogenic lipids (fats), higher blood glucose levels and increased thickness of the carotid arterial walls, which are all potentially associated with premature atherosclerosis.

It is evident that living with perinatally acquired HIV mono-infection is statistically associated with higher morbidity and mortality than in the age-matched general population. In the context of dual infections with either hepatitis B or hepatitis C, plus morbidities associated with the underlying condition for which blood products were required, both survival and quality of life are affected.

A description of the different treatments that have been provided to people infected with HIV and/or AIDS over the years up to the present day (Point 14.10)

Since zidovudine was first licensed in 1987 for the treatment of patients with symptomatic disease, there have been more than 25 antiretroviral drugs licensed for the treatment of HIV-positive adults. Combination antiretroviral therapy (ART; combinations of multiple drugs together) has resulted in marked clinical improvements in the treatment of patients with HIV infection, with some now experiencing near normal life expectancy and many now living well with HIV infection. This section describes the different antiretroviral drug classes, the key landmark studies of ART, current standard of care, when to start ART and drug resistance. It may be helpful to review Figure 1b: The HIV Lifecycle. The following section (14.11) will address in more detail the effectiveness of ART regimens and associated side effects.

i) Drug treatment classes

Nucleoside/nucleotide reverse transcriptase inhibitors

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) are competitive inhibitors of the viral enzyme reverse transcriptase which is responsible for constructing a proviral DNA copy from the single-strand viral RNA (the genetic code of the HIV virus). A proviral DNA copy is required to allow integration of the viral genome into the host cell (CD4+ T helper lymphocyte). Inhibition of viral reverse transcriptase stops the viral replication cycle and thus suppresses viral replication.

The first NRTI to be given regulatory approval and made available to treat patients with HIV/AIDS was zidovudine in mid-1987. The first-generation NRTIs (zidovudine, didanosine, zalcitabine and stavudine) were associated with more severe and often long-lasting side effects including anaemia, nausea, peripheral neuropathy, liver disease and peripheral lipoatrophy. The later NRTIs (lamivudine, abacavir, emtricitabine, tenofovir DF and tenofovir AF) are more tolerable with fewer side effects. Today, a combination of two NRTIs (usually lamivudine and abacavir or emtricitabine and tenofovir DF/AF) forms the backbone of highly active ART regimens which are the current standard of care for treatment of adults with HIV infection.

Non-nucleoside reverse transcriptase inhibitors

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are non-competitive inhibitors of the viral reverse transcriptase enzyme and act by blocking the action of the enzyme in constructing a proviral DNA copy from the single-strand HIV viral RNA. This stops the viral replication cycle and suppresses viral replication.

NNRTIs are one of the options for the third antiretroviral drug in combination with two NRTIs to form triple combination ART. The first NNRTI to receive regulatory approval was nevirapine in early 1998. There are currently five NNRTIs licensed for treatment of HIV infection as part of combination ART. The last to receive approval was Doravirine in 2019. The NNRTIs have been associated with rashes, liver toxicity and neuropsychiatric side effects including sleeping difficulties.

Protease inhibitors

Protease inhibitors (PIs) are competitive inhibitors of the viral enzyme protease. The protease enzyme is responsible for the breakdown of large polyproteins into smaller proteins required for the assembly of new mature viral particles. New immature HIV virions can be produced in the presence of protease inhibitors, but they are unable to infect new cells, in effect blocking the HIV replication cycle, suppressing viral replication.

PIs are used in combination with other antiretroviral drugs, usually two NRTIs, to form triple combination ART. The first PI to receive regulatory approval was ritonavir in August 1996. Although shown to have some clinical benefit in randomised trials, ritonavir was not well tolerated and was quickly superseded by other PIs. Ritonavir is a potent inhibitor of certain liver enzymes and is now only used in lower doses as a pharmacological booster to other protease inhibitors (for example, darunavir, atazanvir). The earlier protease inhibitors (indinavir, nelfinavir, saquinavir and lopinavir) were associated with significant side effects including chronic diarrhoea, nausea and renal stones.

Integrase inhibitors

Integrase inhibitors (INIs) block the activity of the viral enzyme integrase. The integrase enzyme is responsible for the insertion of the HIV proviral DNA into the host cell chromosome which, following cell activation, enables new viral particles to be produced. INIs thus block the replication cycle of HIV, suppressing viral replication.

The first INI to receive regulatory approval was raltegravir in December 2007, the most recent bictegravir (as part of a fixed dose combination tablet) in June 2018. In general, INIs are well tolerated with fewer people discontinuing them due to side effects compared to other antiretroviral drugs. They are used in combination with other antiretroviral

drugs, usually two NRTIs, to form triple combination antiretroviral therapy.

Entry inhibitors

Entry inhibitors stop the virus from entering its target cell. There are two types of entry inhibitors, which currently have regulatory approval for treatment of HIV infection. Enfuvirtide is a fusion inhibitor and received regulatory approval in May 2003. It is given by subcutaneous injection and has mainly been used to treat people with extensive antiretroviral treatment experience with few treatment options due to drug resistance.

Maraviroc blocks the virus from binding to a co-receptor molecule (CCR5) on the surface of the target cell, thus stopping the virus from gaining entry into the cell. It is not commonly used, as it has been shown to be less effective in combination ART compared to other antiretroviral drugs.

ii) Evolution of combination antiretroviral therapy: landmark studies

- **1987:** The first antiretroviral drug, zidovudine, was licensed for treatment of HIV-positive adults with AIDS or non-AIDS symptomatic disease. A clinical trial had shown significant reduction in short-term mortality with zidovudine treatment³² but was associated with significant side effects.

- **1993:** Clinical trials of immediate versus deferred treatment with zidovudine showed no difference in survival benefit at three years of follow-up demonstrating that the initial benefit with monotherapy was short term and time limited.¹¹⁹
- **1996:** Trials of dual NRTI combination therapy showed improved survival and reduced rate of clinical disease progression compared to zidovudine monotherapy.¹²⁰
- **1996:** The development of new classes of ART (PIs and NNRTIs) allowed assessment of triple combination therapy containing two NRTIs and a third agent. Initial studies showed triple combination therapy resulted in higher and more prolonged rates of viral suppression with greater increases in CD4 count compared to dual NRTI therapy. Highly active ART was first termed 'HAART'.
- **1997:** A trial of the PI indinavir with two NRTIs (triple combination therapy) demonstrated improved clinical benefit compared to treatment with two NRTIs alone.⁴⁹
- **1997:** Analysis of several large clinical end point studies showed changes in plasma viral load and CD4 count were predictive of clinical outcome, establishing changes in these surrogate markers as outcome measures for future assessment of new antiretroviral drugs and regimens.

- **1997:** British HIV Association guidelines for the treatment of adults with HIV-1 infection were first published.⁵⁰ An update in 1998 recommended patients start highly active ART with two NRTIs in combination with either a PI or a NNRTI.
- **1997–2007:** During this period of time, multiple new antiretroviral drugs were licensed which were associated with significant improvements in efficacy, safety and tolerability of combination ART.
- **2006:** The SMART trial reported the importance of continued viral suppression to improve clinical outcome.¹²¹ A strategy of continued use of ART resulted in better clinical outcomes compared to a strategy of periodic treatment guided by CD4 count. The study also for the first time showed benefit in terms of reducing non-HIV-associated comorbidities with continued ART.
- **2007:** Raltegravir, a drug from a new class of ART, the INIs, was first licensed in December **2007:** Studies had demonstrated significant benefit in ART-experienced patients with HIV drug resistance.
- **2011:** In a study of HIV-discordant partners, early ART resulted in a 96% reduction in risk of HIV transmission between the HIV-positive and HIV-negative partner. These results established the importance of ART as treatment as prevention.⁶⁷
- **2013:** Dolutegravir (an INI) in combination with abacavir and lamivudine was shown to

have superior efficacy in terms of virological suppression than a combination of efavirenz, emtricitabine and tenofovir DF, the standard of care regimen at the time.¹²² The improved efficacy was largely driven by tolerability and reduced rates of drug discontinuation of the dolutegravir-containing regimen.

- **2015:** The START trial showed starting therapy immediately in early disease, irrespective of CD4 count, was associated with improved clinical benefit compared to deferring treatment till the CD4 count had fallen.¹²³ Clinical guidelines universally changed to recommend HIV-positive adults start ART irrespective of CD4 count.
- **2019:** Public Health England report that in the UK, of patients attending for HIV care, 97% are on ART of whom 97% have undetectable viral loads reflecting the excellent treatment outcomes in terms of virological efficacy that has been achieved.

iii) Current standard of care

The British HIV Association (BHIVA) clinical guidelines for treatment of adults with HIV infection with ART outline best clinical practice in the UK. Recommendations are based on evidence from clinical studies including randomised clinical trials. BHIVA guidelines are accepted by healthcare professionals providing treatment and care for HIV-positive patients

in the UK as the national reference document for good clinical practice. The process by which BHIVA produces its clinical guidelines has since 2012 been approved by the National Institute for Health and Care Excellence (NICE).

The BHIVA ART guidelines were first published in April 1997 and recommended starting ART with at least dual NRTI therapy. The guidelines were updated in July 1998 and recommended HAART for all patients with two NRTIs and either an NNRTI or a PI. The guidelines have since been updated at regular intervals to take into account new evidence of best practice. The last revision was published in 2016 with an interim statement in 2019. 10 Other international guidelines which help to inform best practice include those from the European Clinical AIDS Society (EACS) and from the International AIDS Society (USA).

The current BHIVA-recommended regimens (preferred and alternative) are detailed in Table 5 and are largely similar to other international clinical guidelines. Patients newly diagnosed with HIV infection are currently most commonly started on a regimen containing two NRTIs (emtricitabine and tenofovir DF/Tenofovir AF or lamivudine and abacavir) and an INI due to fewer side effects, better tolerability and higher virological efficacy compared to other regimens. Treatment regimens for ART-experienced patients will depend on previous intolerance and virological failure to antiretroviral drugs, and the presence of HIV drug resistance.

iv) When to start antiretroviral therapy

The early trials of ART largely investigated efficacy in patients with AIDS or non-AIDS symptomatic disease with low CD4 counts as these patients were most in need of effective therapy. Compared to patients with asymptomatic disease and higher CD4 counts, those with symptomatic disease had significantly higher rates of clinical disease progression and death. Once the CD4 count falls to below 200 cell/uL, the risk of clinical disease progression increases rapidly. For this reason and because of the risk of drug side effects and treatment emergent drug resistance, earlier versions of the BHIVA guidelines recommended starting therapy before the development of significant immune deficiency, at a CD4 count of between 200 and 300 cell/uL, later increased to around a CD4 count of 350 cell/uL. These recommendations were largely based on expert opinion, an understanding of risk of clinical disease progression, and the known efficacy and safety of ART at the time.

Previously, trials of zidovudine monotherapy, first reported in 1993, had shown no difference in survival or progression to AIDS at three and five years of follow-up in patients who started therapy immediately, compared to deferring starting therapy till they had developed symptomatic disease or when their CD4 count had fallen. Although immediate treatment with zidovudine did result in clinical benefit, this was short term and time limited. There was no difference in

survival rates for both treatment strategies at three years of follow-up.

It was not until 2015 that definitive evidence was first presented that immediate treatment with combination ART was associated with clinical benefit, irrespective of baseline CD4 count. In this study, patients with asymptomatic disease and a CD4 count above 500 cell/uL were randomised to either start ART immediately or defer till their CD4 counts had fallen towards 350 cell/uL or they had developed symptomatic disease. The study showed that even in this population, who had low risk of clinical progression, starting ART immediately resulted in a greater than 50% reduction in clinical progression to either any serious AIDS-related event, serious non-AIDS-related event or death from any cause compared to the deferred therapy group. The primary end point occurred in 1.8% (0.60 events per 100 person years) in the immediate group versus 4.1% (1.38 events per 100 person years) in the deferred group. Clinical benefit was seen across all strata of CD4 counts. Importantly, risk of adverse events was no different between the two groups, establishing the safety of starting ART in early disease.

As a result of these study findings, BHIVA updated their treatment guidelines in 2015⁷³ and recommended that patients with HIV start ART irrespective of CD4 count. They had previously recommended in 2013 that patients with a risk of onward transmission of

HIV should consider starting ART, as treatment as prevention, irrespective of CD4 count. In April 2018, NHS England published a clinical commissioning policy ('Immediate ART') stating that all patients with HIV infection should be recommended to start ART irrespective of CD4 count or risk of onward transmission.

Although starting ART in early disease is preferable, many patients are diagnosed late when their CD4 counts have already fallen to <350 cell/uL. In 2018, 43% of patients newly diagnosed had a CD4 count of 350 cell/uL or less. The proportion was higher in certain sub-populations such as black African adults and those aged 50 years of age or older.

v) Drug resistance

In the early clinical trials of mono and dual NRTI therapy, clinical benefit was shown to be time limited. Viral isolates grown from blood taken from patients who had been treated for more than six months of zidovudine were shown to have markedly reduced susceptibility to the antiviral effect of zidovudine in vitro. Subsequent tests showed that these viral isolates had multiple mutations in the viral gene responsible for the coding of viral enzyme reverse transcriptase.¹²⁴ These viral mutations conferred high-level resistance to zidovudine.

In patients treated with mono or dual NRTI therapy, the viral load in blood initially falls as a consequence of the antiviral effect of the drugs but, then after a few months or more, starts to increase back to pre-treatment levels. This rise in viral load is temporally associated with the emergence of mutations in the viral genome, which results in viral resistance to the action of the drugs. Virological failure and the emergence of drug resistance are secondary to inadequate virological potency and the failure to suppress viral load to undetectable levels. HAART is more effective as it usually results in optimal suppression of viral replication and thus viral load which, as long as the patient is adherent to therapy, is maintained over time, preventing the emergence of drug resistance.

Viral mutations causing drug resistance have been identified with all currently licensed antiretroviral drugs. With some drugs, a single viral mutation causes high fold resistance (low genetic barrier – for example, lamivudine, nevirapine), whilst with other drugs the accumulation of multiple mutations over time is required or the development of resistance mutations is rare (high genetic barrier – for example, boosted PIs, dolutegravir, bictegravir). Viral mutations are associated with cross-resistance to other drugs in the same class and remain present in HIV-infected long-lived T lymphocytes. If patients are re-exposed to the same drugs, then these mutations can quickly re-emerge. Viral mutations can also be transmitted.

In patients newly diagnosed with HIV in the UK, approximately 8% have transmitted drug resistance.

Many patients who were treated with mono or dual NRTI therapy and the earlier HAART regimens experienced virological failure and developed resistance to one or more classes of antiretroviral drugs. In these treatment-experienced patients, treatment options were limited due to drug resistance. However, with the advent of INIs and the newer boosted PIs with high genetic barriers, nearly all treatment-experienced patients with previous drug resistance can be treated with effective antiretroviral regimens. The main factor associated with virological failure and emergence of drug resistance viral mutations on HAART regimens is non-adherence to therapy.

With the current recommended ART regimens, efficacy and tolerability are high. As long as patients are adherent to their medication, then virological failure and emergence of drug resistance are very uncommon.¹²⁵

An analysis of the predictive factors in establishing the likelihood of treatment being successful (Point 14.11a)

Predictive factors of treatment outcome include both HIV- and patient-related factors. HIV-related factors include baseline CD4 count and viral load, drug resistance and stage of disease.

Patients with high baseline viral load ($>100,000$ copies/ml), low CD4 counts (<200 cell/uL) and symptomatic disease, particularly a previous AIDS diagnosis, have had in general poorer treatment outcomes compared to patients starting ART with lower viral loads, higher CD4 counts and in early disease. The efficacy of ART in terms of viral suppression has frequently been reported to be lower in patients with high baseline viral loads, this is largely related to the longer time for plasma viral load to fall to less than <50 copies/ml and the virological potency of antiretroviral regimen. However, with the more modern ART regimens which include an INI, rates of viral load suppression are similar for patients with a baseline viral load above 100,000 copies/ml or a CD4 count below 200 cell/uL.

Patients who start ART in advanced disease, with CD4 counts less than 200 cell/uL or lower, continue to have a higher risk of new AIDS diagnosis or death for up to

two to three years from the start of ART than patients starting ART with a CD4 count >350cell/uL.

The incidence of side effects and tolerability of ART regimens, particularly the older ART regimens, is higher in patients with advanced disease including AIDS. This is largely related to the fact that they are unwell with symptomatic disease and have a more limited capacity to tolerate side effects. However, the tolerability of INIs containing regimens is high, even in patients with AIDS and severe immune deficiency or those requiring chemotherapy.

Of demographic factors, only older age has been consistently associated with poorer treatment outcomes and this is likely to be related to high risk of disease progression and a higher prevalence of non-AIDS comorbidities. Neither gender nor race are generally associated with poorer outcomes if access to care and tolerability of regimens are taken into account.

The most important patient-related factor predictive of treatment outcome is adherence. Non-adherence to ART is associated with treatment failure and emergence of HIV drug resistance. In general, high levels of adherence to a treatment regimen (>90%) are required to maintain virological suppression, though this may vary between different regimens. Factors that have an impact on ability to adhere to therapy includes the number of pills and dosing frequency

of ART regimens, side effects of medication, mental health problems such as depression and anxiety, social welfare factors such as housing and financial difficulties, and co-morbidities. Supporting patients to adhere to their ART regimens is an essential part of HIV care. Fewer pills, once-daily dosing and improved tolerability of current ART regimens have helped to improve adherence.

Supplementary Question 16

If patients stop therapy, then blood viral load rebounds towards pre-treatment levels within one month of therapy discontinuation. ART unfortunately does not eliminate HIV infection: it very effectively reduces HIV replication to very low levels and maintains effective inhibition of viral replication over time, allowing reconstitution of the immune system. Once therapy is stopped, viral replication increases to pre-treatment levels, causing progressive damage to the immune system and ultimately severe immune deficiency and the clinical disease associated with this. Usually the CD4 count will fall to pre-treatment levels within six months of stopping ART and will continue to fall unless ART is restarted. For these reasons, ART needs to be taken lifelong. There is a significant amount of ongoing research, investigating HIV cure and eradication strategies.

An analysis of how effective the various treatments have been over the years for people infected with HIV and /or AIDS (Point 14.11b)

The effectiveness of early mono and dual therapy regimens was low and time limited. In the first randomised clinical trial of zidovudine monotherapy (reported in 1987) in patients who had advanced disease with AIDS or non-AIDS symptomatic disease, at a median of four months of follow-up <1% of patients who received zidovudine had died compared to 14% of patients who received placebo.³² However, this clinical benefit was not sustained and mortality remained high in clinic populations. Treatment benefit was limited by side effects and the development of drug resistance.

Randomised clinical end point trials of dual therapy (first reported in 1995) compared zidovudine monotherapy versus a combination of zidovudine with either didanosine or zalcitabine and showed a relative reduction in mortality of between 30% and 40% with dual therapy compared to zidovudine alone over a median of 30 months' follow-up. Clinical benefit was sustained out to two to three years of treatment.⁶⁷ Despite this improvement, mortality in this patient population with advanced disease remained high with approximately one in five patients who received dual therapy dying over the duration of the study. A further

one in three patients experienced clinical disease progression.

It was not until the development of HAART (first reported in 1996) did we see sustained virological suppression and improvements in the immune system associated with long-term clinical benefit. The advent of HAART had a major impact on reducing mortality and clinical progression. The development of new classes of ART, the PIs and the NNRTIs, allowed the investigation of triple combination therapy regimens with two NRTIs in combination with a third agent, either a PI or a NNRTI. Studies of the PI indinavir in combination with lamivudine and either zidovudine or stavudine showed improved survival and reduced clinical progression compared to dual therapy. Higher proportion of patients achieved virological suppression at one year on triple therapy compared to dual therapy.⁴⁹

These clinical end point studies also established that changes in plasma viral load and CD4 count were predictive of clinical outcome. Thus, in subsequent clinical trials, changes in these surrogate markers were used to assess efficacy of different regimens. Rises in CD4 count and proportion of patients achieving virological suppression at 48 and 96 weeks became standard outcome measures for investigating efficacy of new antiretroviral drugs and regimens.

Over the next 10 to 15 years with the development of newer PIs (used with ritonavir as a booster) and newer NNRTIs, the efficacy, safety and long-term tolerability of HAART regimens continued to improve significantly. In 1998, a study of a regimen containing efavirenz, zidovudine and lamivudine reported that 64% of patients achieved an undetectable viral load of <50 copies/ml at 48 weeks of therapy. Similar results were reported in 2002 with a combination of lopinavir (boosted with ritonavir), stavudine and lamivudine. The boosted PIs were also associated with a lower risk of HIV drug resistance at virological failure.

A large randomised clinical trial comparing efavirenz versus lopinavir/ritonavir each in combination with two NRTIs reported (in 2008) a longer time to virological failure with the efavirenz containing regimen. At 96 weeks, the proportion of patients with a viral load <50 copies/ml was 89% with the efavirenz containing regimens versus 77% with lopinavir/ritonavir.¹²⁵ This established efavirenz in combination with two NRTIs as the standard of care for several years after.

Abacavir and tenofovir DF emerged as replacements for stavudine and zidovudine due to better tolerability and safety profiles. Abacavir in combination with lamivudine and tenofovir DF (or tenofovir AF) with emtricitabine continue to be recommended as NRTI backbones in combination with a third agent in current clinical guidelines.

Raltegravir was the first INI to be licensed in 2007 and, together with the newer PI darunavir (boosted with ritonavir), significantly improved the treatment outcome of patients who had experienced virological failure on previous regimens and had developed dual or triple class HIV drug resistance. These patients previously had limited treatment options. Now most ART-experienced patients with history of virological failure, drug resistance and/or treatment intolerance can be treated with effective combination regimens.

INIs have been shown to have similar virological efficacy to PIs or efavirenz containing triple regimens but overall are more effective due to better tolerability and lower discontinuation rates from adverse events. In 2013, a combination of dolutegravir, abacavir and lamivudine was shown to have significantly higher rates of viral suppression compared to a combination of efavirenz, tenofovir DF and emtricitabine (89% versus 81% at 96 weeks).¹²² The difference was largely attributable to a lower discontinuation rate secondary to adverse events in the dolutegravir arm (2%) compared to the efavirenz arm (10%). In national and international clinical guidelines, INIs containing combination regimens have largely become the preferred treatment of choice in patients starting ART for the first time due to higher virological efficacy and tolerability compared to other regimens.

With the current recommended antiretroviral regimens, patients who adhere to their therapy can expect to

experience sustained virological suppression with undetectable viral loads in blood with limited risk of virological failure and emergent drug resistance. Data from Public Health England show that, in the UK in 2018, 97% of patients receiving HIV care were on antiretroviral therapy of whom 97% had undetectable viral loads. Sustained virological suppression and immune reconstitution has resulted in marked improvements in life expectancy and reduction in HIV-associated co-morbidities, with reports of near normal life expectancy in patients starting therapy in early disease. Further data on life expectancy is outlined in Point 14.14.

However, despite these excellent treatment outcomes, people living long term with HIV infection on ART experience an increased prevalence of non-AIDS comorbidities, including those associated with ageing such as cardiovascular and chronic kidney disease and an increased incidence of certain cancers (such as lymphoma and lung cancer) compared to an aged matched HIV negative population. Quality of life is frequently impacted by a higher prevalence of mental health disorders, chronic musculoskeletal symptoms, metabolic disorders and frailty.

A description of what is known about the short- and long-term impact of those treatments (Point 14.12)

The earlier antiretroviral drugs were associated with significant short- and long-term side effects, often treatment limiting or frequently having an impact on quality of life. The tolerability and dosing convenience of ART regimens have significantly improved over time with much lower rates of discontinuation due to adverse events. The reported efficacy and adherence to current recommended treatment regimens are high. However, like all medication, side effects do occur with all antiretroviral drugs and can affect tolerability and have an impact on quality of life.

Common side effects (as defined by a prevalence of greater than 1/100 patients) associated with individual drugs are listed in Table 4.

Common short-term side effects, mainly with the older antiretroviral drugs, include: gastrointestinal symptoms (nausea, vomiting, diarrhoea), hypersensitivity reactions (fever and rash), neuropsychiatric (insomnia, abnormal dreams, low mood, anxiety, headaches), hepatitis (abnormal liver function), asthenia and fatigue. Some of these would have been severe enough to cause treatment discontinuation; others contributed to

low-grade symptoms which had a negative impact on quality of life.

One potential adverse effect of ART is immune reconstitution inflammatory syndrome (IRIS) which, although not a direct effect of drugs, is a consequence of HIV infection mainly seen in patients with AIDS and severe immune deficiency starting ART. In advanced HIV disease, the ability of the immune system to effectively fight infections is lost. Infections that have previously been kept in check through immune surveillance re-activate and cause disease. Treatment with ART results in reconstitution of the immune system allowing the immune system to once again recognise and fight infection. The clinical impact of this is that patients may become ill (occasionally severely or to the point where life is threatened) within a few weeks of starting ART with symptoms of an opportunistic infection (for example, mycobacterial disease) which they may have previously been treated for or had been undiagnosed and are asymptomatic from. With continued treatment with ART, IRIS generally resolves but can cause quite severe ill health at the time. Approximately 10% of patients with very advanced disease ($CD4 < 50$ cell/uL) develop IRIS within the first few weeks of starting ART.

Several severe and frequently disabling side effects have been associated with long-term use of ART, most commonly with the first-generation antiretroviral drugs.

Lipodystrophy, a fat redistribution disorder which included peripheral lipoatrophy and lipohypertrophy was commonly seen with the older ART regimens. Peripheral lipoatrophy (loss of subcutaneous fat) was common with the first-generation NRTIs (zidovudine, stavudine, zalcitabine and didanosine). This particularly affected the face and limbs and resulted in disfigurement, stigma and anxiety. Lipoatrophy improves on discontinuation of these NRTIs, but many patients exposed to these drugs in the past continue to require treatment with facial fillers at regular intervals to help improve psychological and physical wellbeing.

Lipohypertrophy (fat accumulation) usually presented with increased visceral fat in the abdomen resulting in abdominal distension and swelling. It is also associated with fat accumulation at the base of the neck (buffalo hump) resulting in disfigurement. Lipohypertrophy was largely reported with the first-generation PIs such as indinavir. Aetiology, however, is complex and discontinuation of the PI does not result in improvement. Increased visceral fat is often seen in the general population with ageing. It is generally not seen with the newer PIs atazanavir and darunavir. Increased visceral fat is associated with increased risk of diabetes and liver disease.

Peripheral neuropathy is a complication of HIV infection and usually presents as numbness and pins and needles in the feet and lower legs and largely improves over time with treatment of HIV infection.

However, some of the earlier NRTIs also caused a drug-associated peripheral neuropathy which was frequently painful and difficult to treat. Despite discontinuation of the specific NRTI, symptoms often persisted for many months and years.

Other conditions associated with long-term treatment with ARVs include chronic liver disease, exocrine pancreatic deficiency, low bone mineral density and chronic kidney disease. Some of these have been associated with significant disability and chronic symptoms.

Nearly all the examples of side effects of treatment described in witness statements can be found in the list of common side effects in Table 4 and/or have been described earlier. There is no doubt that in many patients side effects from medication, particularly from the older ART regimens, significantly affected their quality of life on a daily basis. However, it should also be noted that many of these symptoms may also be associated with symptomatic HIV disease. Constitutional symptoms, such as weight loss, diarrhoea, poor appetite and fatigue, are common in patients presenting with symptomatic disease. Peripheral neuropathy, dermatitis, blood disorders such as anaemia, gingivitis and periodontal disease, and memory difficulties are well-recognised complications of symptomatic HIV infection. These problems would generally resolve with time with effective ART and improvement of the immune system. Those symptoms

occurring for the first time or worsening on starting ART would more likely to be side effects from medication.

Although side effects are common, the long-term benefit of antiretroviral therapy in terms of improved survival and decreased HIV associated co-morbidities generally outweighs potential harm. In 2006, a large randomised trial comparing a treatment strategy of continued use of ART to maintain viral suppression with a strategy of episodic use of ART, guided by CD4 count (drug conservation arm), reported better clinical outcomes with continued viral suppression.¹²¹ Rates of death from any cause and new opportunistic disease were significantly lower in the viral suppression arm and, importantly, there was no difference in the rate of adverse events between the two treatment strategies. In addition, continued viral suppression reduced the incidence of major non-HIV-related co-morbidities (cardiovascular, renal and hepatic diseases). The study established the importance of continued viral suppression from ART in reducing both HIV and non-HIV-associated clinical disease. These results do not, however, minimise the impact treatment-related side effects can have on quality of life. Many trials of ART have not reported on quality of life outcomes. Although long-term treatment with ART is essential in improving survival and preventing disease progression, maintaining good quality of life is equally important.

The more modern antiretroviral regimens have good tolerability, low rates of discontinuation (<5%) due to adverse events at one year of treatment and few known long-term side effects. Efficacy in terms of virological suppression at one year is high (>90%).

Table 3: BHIVA guidelines: summary recommendations for choice of ART 2016⁷³

	Preferred	Alternative
NRTI backbone	Tenofovir DF and emtricitabine Tenofovir AF and emtricitabine	Abacavir and Lamivudine
Third agent (alphabetical order)	Atazanvir/r Darunavir/r Dolutegravir Elvitegravir/c Raltegravir Rilpivirine /r: boosted with ritonavir /c: boosted with cobicistat	Efavirenz

Table 4: Common side effects associated with antiretroviral drugs

Table note: The list has been sourced from the summary of product characteristics for each antiretroviral drug. The list is not exhaustive but reflects those symptoms commonly reported in clinical trials or clinic populations. Enfuvirtide, maraviroc and tipranavir have not been included as they have been used infrequently.

Antiretroviral drug	Regulatory approval	Common side effects (>1/100 persons)	Comment
Nucleoside/nucleotide reverse transcriptase inhibitors			
Zidovudine	March 1987	Blood disorders: anaemia, neutropaenia Nausea, vomiting, diarrhoea, abdominal pain Headache, malaise, dizziness Myalgia Lipoatrophy (subcutaneous fat loss)	Side effects were common and often treatment limiting, particularly with the higher dose earlier treatment schedules. Lipoatrophy was common with long term use.
Didanosine	June 1992	Lipoatrophy Peripheral neuropathy Headache Nausea, diarrhoea, abdominal pain, flatulence, dry mouth Hepatitis Fatigue, asthenia Rash Joint and muscle pain	Earlier formulations of didanosine were very commonly associated with gastrointestinal side effects and frequently treatment limiting. Painful peripheral neuropathy was very common with long term use. Pancreatitis and severe liver disease (including non-cirrhotic portal hypertension) have been associated with long-term use.
Zalcitabine	September 1994 Withdrawn December 2006	Peripheral neuropathy Headaches, dizziness Nausea, vomiting, abdominal pain, oral ulcers Pancreatitis	Painful peripheral neuropathy was a common problem on long-term use and symptoms persisted long time after discontinuation. Pancreatitis and liver disease have been associated with long term use.

Antiretroviral drug	Regulatory approval	Common side effects (>1/100 persons)	Comment
Stavudine	May 1996	Lipoatrophy Peripheral neuropathy Insomnia, headache Nausea, diarrhoea, abdominal pain Rash	Lipoatrophy and painful peripheral neuropathy were very common with long term treatment with stavudine. Severe pancreatic and liver disease have been associated with long term use.
Lamivudine	August 1996	Insomnia, headaches Nausea, diarrhoea, abdominal pain Rash, hair loss Joint and muscle pain Cough, nasal symptoms	Rates of drug discontinuation are low. Long term treatment is generally well tolerated.
Abacavir	July 1999	Hypersensitivity reaction (rash, fever, systemic symptoms) Nausea, vomiting, diarrhoea, poor appetite Headache Lethargy, fatigue	Gastrointestinal side effects usually occur in the first few weeks of treatment and often then settle.. Abacavir is generally well tolerated in the long term but has been associated with increased risk of cardiovascular disease.
Tenofovir disoproxil	February 2002	Headache, dizziness Nausea, vomiting, diarrhoea, abdominal pain, flatulence Hypophosphataemia Rash Fatigue, asthenia	Long term use is associated with renal toxicity (proximal renal tubulopathy), loss of bone mineral density, and increased risk of chronic kidney disease.

Antiretroviral drug	Regulatory approval	Common side effects (>1/100 persons)	Comment
Emtricitabine	October 2003	Allergic reaction. Insomnia, headaches, dizziness Nausea, diarrhoea, abdominal pain Skin pigmentation Hepatitis	Long term treatment is generally well tolerated.
Tenofovir Alafenamide	April 2016	Nausea, vomiting, diarrhoea, abdominal pain, flatulence Headache, dizziness, abnormal dreams Rash Fatigue	Only available in a co-formulation tablet with other antiretroviral drugs. Compared to tenofovir DF, tenofovir AF has not been associated with loss of bone mineral density and renal toxicity is rare. Long term tolerability is generally good.
Non-nucleoside reverse transcriptase inhibitors			
Nevirapine	February 1998	Hypersensitivity reaction (fever, rash, hepatitis) Headache Nausea, vomiting, diarrhoea Hepatitis.	In the first few weeks of treatment severe life threatening skin reactions and hepatitis have occurred. In the long term nevirapine is well tolerated with few side effects.
Efavirenz	May 1999	Insomnia, abnormal dreams, anxiety, depression Headache, dizziness, somnolence Nausea, vomiting, diarrhoea Transaminitis (abnormal liver function tests) Rash Fatigue	More than any other antiretroviral drug, neuropsychiatric symptoms were common with efavirenz and were the main reason for treatment discontinuation over time. Increased risk of suicidality has been reported. Gynaecomastia reported with long-term use.

Antiretroviral drug	Regulatory approval	Common side effects (>1/100 persons)	Comment
Etravirine	August 2008	Rash, hypersensitivity reaction Sleep disorders, insomnia, anxiety Headache Transaminitis (abnormal liver function tests)	Safety profile similar to other NNRTIs within class. Neuropsychiatric symptoms less common.
Rilpivirine	November 2011	Insomnia, abnormal dreams, depression Headache, dizziness Nausea Rash Transaminitis	Generally well tolerated with long term use with low discontinuation rate due to adverse events. Incidence and grade of neuropsychiatric symptoms much lower compared to other NNRTIs.
Protease inhibitors			
Ritonavir	August 1996	Nausea, vomiting, diarrhoea, abdominal distension, flatulence, abdominal pain Hyperlipidaemia Lipodystrophy Oral and peripheral paraesthesia Hepatitis Headache, dizziness, rash	Ritonavir was first licensed as an antiretroviral drug, but intolerable gastrointestinal side effects at treatment doses limited use. Has subsequently been used as a pharmacokinetic booster for other PIs.

Antiretroviral drug	Regulatory approval	Common side effects (>1/100 persons)	Comment
Indinavir	October 1996	Headaches, dizziness, insomnia Nausea, vomiting, diarrhoea, dry mouth Hyperbilirubinaemia, abnormal liver function Lipodystrophy Renal stones (associated with renal impairment) Fatigue, asthenia Rash, dry skin Muscle pain Hyperlipidaemia	Indinavir was first used without ritonavir boosting and was difficult to adhere to, in view of its dosing schedule. Renal stones and chronic kidney disease were common with long term use. Central adiposity was a common and disfiguring long term side effect. Increased risk of bleeding reported in haemophiliacs No longer recommended in guidelines
Saquinavir	October 1996	Nausea, vomiting, diarrhoea, abdominal distension Transaminitis (abnormal liver function tests) Headache, dizziness Hyperlipidaemia Lipodystrophy	Saquinavir was first used with ritonavir as a booster and had a high pill burden. Like all first generation PIs gastrointestinal side effects were very common and often led to drug discontinuation. Increased risk of bleeding reported in haemophiliacs No longer recommended in guidelines
Nelfinavir	January 1998 Withdrawn 2013.	Nausea, vomiting, diarrhoea, flatulence Rash Hyperlipidaemia Lipodystrophy Transaminitis (abnormal liver function tests)	Gastrointestinal side effects were very common, with up to 50% of patients experiencing diarrhoea. Nelfinavir was withdrawn in 2013.

Antiretroviral drug	Regulatory approval	Common side effects (>1/100 persons)	Comment
Lopinavir	March 2001	Nausea, vomiting, diarrhoea, abdominal distension, abdominal pain Hyperlipidaemia Hepatitis Rash, hypersensitivity reactions Headache, dizziness Lipodystrophy	Gastrointestinal symptoms were very common in particular diarrhoea. Has largely been replaced by atazanavir and darunavir.
Atazanavir	March 2004	Hyperbilirubinaemia, jaundice Rash Nausea, diarrhoea, abdominal pain Headache	Long term use associated with renal stones and increased risk of chronic kidney disease. Lower level of gastrointestinal symptoms compared to earlier PIs.
Fosamprenavir	July 2004	Nausea, vomiting, diarrhoea Rash Hyperlipidaemia Headache Transaminitis	As with other PIs gastrointestinal side effects were common. No longer recommended in guidelines
Darunavir	February 2007	Nausea, diarrhoea, abdominal pain, abdominal distension Rash, hypersensitivity Transaminitis (abnormal liver function tests) Headache, dizziness	Currently most common PI used in ART treatment regimens. Generally well tolerated in the long term, low grade gastrointestinal side effects may occur.
Integrase inhibitors			

Antiretroviral drug	Regulatory approval	Common side effects (>1/100 persons)	Comment
Raltegravir	December 2007	Insomnia, abnormal dreams, depression Headaches dizziness, vertigo Rash Loss of appetite, nausea, diarrhoea Tiredness	Severity of side effects is generally low and frequently settle in the first few weeks of treatment. Discontinuation rates are low.
Elvitegravir	May 2013	Abnormal dreams Nausea, diarrhoea, Headache, dizziness Rash	Only available in co-formulated tablet with cobicistat, emtricitabine and tenofovir DF/AF. Generally well tolerated with low discontinuation rates, though use has been more limited compared to other integrase inhibitors.
Dolutegravir	January 2014	Insomnia, abnormal dreams, depression, anxiety Headache, dizziness Nausea, diarrhoea Rash	Generally well tolerated in the long term, though neuropsychiatric side effects have emerged as a problem with some patients.
Bictegravir	June 2018	Abnormal dreams, depression Headache, dizziness Nausea, diarrhoea	Only available in co-formulated tablet with emtricitabine and tenofovir AF. Well tolerated in clinical trials with low discontinuation rate from adverse events reported. Data on long term tolerability in clinic populations is limited.

The prognosis and life expectancy of people infected with HIV and how this has changed over the years (Point 14.14 and Supplementary Question 9)

The general aspects of prognosis and life expectancy have been summarised above under Point 14.3. In summary, an average of 8 to 10 years pass, in the natural course of HIV following initial infection, before AIDS-defining events occur. Without antiretroviral therapy (ART), usually these illnesses lead to death within two years. Factors which drive disease progression as outlined above are level of HIV-viremia and age. The introduction of highly active ART in 1996 was able to dramatically change life expectancy in the setting of achieving persistent suppression of viral replication.⁴⁹ With the introduction of better tolerated drugs, introduction of longer drug half-lives and fixed dose formulations, life expectancy has continued to increase substantially. If ART is started early enough, life expectancy approaches that of the general population as demonstrated in the Swiss cohort.¹²⁶ This was also demonstrated in the Antiretroviral Therapy Cohort Collaboration. In their analysis, even in the late ART era, survival during the first three years of ART continues to improve, which probably reflects transition to less toxic antiretroviral drugs, improved

adherence, prophylactic measures and management of comorbidity.¹¹³

(a) Does early diagnosis and/or treatment make a difference to prognosis and/or life expectancy? If so, is there is an optimum period of time within which a person should receive treatment? Has this differed over time?

Many cohorts have shown that improving life expectancy depends on the time point of starting combination ART. Initial studies after introduction of potent ART demonstrated that patients with presumed transmission via injecting drug use had lower life expectancies than did those from other transmission groups.¹²⁷ Life expectancy was lower in patients with lower baseline CD4 cell counts than in those with higher baseline counts, in particular for CD4 cell counts below 100 cells. Moreover, normalisation of T4/T8 ratio appears mostly only achievable upon early ART initiation and has been associated with a lower risk for non-AIDS-defining events.¹²⁸

(b) Is the prognosis or life expectancy different for a person who is co-infected with HCV and/or HBV compared to a person infected solely with HIV?

The life expectancy for patients infected with HIV and additional hepatitis B and/or C coinfection is different due to the increased risk of dying from concomitant liver disease. Indeed, within the EuroSIDA cohort, patients with hepatitis C antibodies had a nine-fold

higher risk of dying from liver disease which was even higher in the presence of detectable hepatitis C replication.¹²⁹ Similarly, data from the UK demonstrated increased rates of all-cause and liver-related mortality among individuals with hepatitis B or C co infection as well as HIV infection, highlighting the need for primary prevention and access to effective hepatitis treatment for HIV-positive individuals.¹³⁰ Neither hepatitis B nor hepatitis C coinfection were associated with increased AIDS-related mortality.

Co-infections with hepatitis: what is the significance, in terms of symptoms, impact and treatment, of co-infection with (a) HBV and/or (b) HCV and/or (c) other viruses? (Point 14.15)

Because of the increased risk of dying from liver disease in the setting of chronic hepatitis coinfection, in particular with progredient immunodeficiency,¹³¹ treatment of underlying hepatitis B and C is of utmost importance. Whereas early in the HIV epidemic, there were no satisfactory treatment options for HBV or HCV, this has fortunately dramatically changed over time (see also Expert Report to the Infected Blood Inquiry: Hepatitis).

Although successful antiviral combination therapy for HIV and subsequent immune reconstitution can slow down the faster fibrosis progression in HCV coinfection, risk of hepatic decompensation still remains higher in ART-treated HIV/HCV coinfecting individuals versus HCV-monoinfected subjects.¹³² Sustained virological response (SVR) or cure after interferon (IFN) and ribavirin (RBV) combination therapy tended to be significantly lower in HIV-coinfecting individuals particularly in genotype 1 patients. Therefore, the EACS guidelines recommended longer treatment durations of up to 72 weeks for genotype 1 and 4 patients who still had a detectable HCV-RNA four weeks after starting HCV therapy and at least a >2 log drop in HCV-RNA at week 12 of HCV therapy.¹³³ Treatment for genotype 2 and 3 could last up to 48 weeks. Considering the longer HCV treatment durations, a higher risk for cumulative interferon and ribavirin related toxicity existed for HIV coinfecting individuals. In the era of all oral direct acting anti-viral combination therapy, similar SVR rates have been observed for HIV-coinfecting and HCV-monoinfected subjects.¹³⁴ For HBV coinfection, a tenofovir-containing ART has become the standard of care with similar good outcomes as in treatment of HBV mono-infection. Hepatitis delta superinfection in patients with HIV/HBV coinfection remains a tremendous challenge as liver fibrosis progression is fastest and risk of dying from liver disease is particularly high. Unfortunately, treatment options

are still poor in hepatitis D and usually consist of interferon-based strategies.

Impact of bleeding disorders (Point 14.16 and Supplementary Question 10)

To what extent, and how, does HIV affect people with:

(a) haemophilia, (b) von Willebrand disease, (c) thalassaemia and (d) sickle cell anaemia differently from those who do not have a bleeding or blood disorder?

The impact of HIV on people with haemophilia, their families and the services providing specialist care has been profound and multifactorial.^{135, 136} This response focusses specifically on the clinical issues.

Overall, the clinical course of HIV and AIDS is not greatly affected by transmission risk group. The US National Cancer Institute evaluated the age-specific relative risk of progression from HIV seroconversion to onset of AIDS in people with haemophilia and homosexual men.¹⁰¹ Prospective follow-up data from HIV seroconversion to AIDS was analyzed for people with haemophilia in the Multicenter Hemophilia Cohort Study and for homosexual men in the International Registry of Seroconverters. Follow-up was censored at 1 July 1987 to obtain natural history estimates unaffected by therapies that were widely used after this date. The age-specific relative hazard of progression was estimated using nonparametric proportional hazards models and the baseline hazard

function was described using spline models. Among the 373 children and adults with haemophilia and the 1020 adult homosexual men, each 10-year increment in age at seroconversion was associated with a 1.6- and 1.4-fold increase in the hazard of progression, respectively.¹⁰¹ The effect of age was highly significant among people with haemophilia. The magnitude of the effect was consistent in different cohorts of homosexual men, although it was not nominally significant. Furthermore, there was a significant increase (1.9-fold higher) in progression rates among homosexual men above rather than below 35 years of age at seroconversion. After adjusting for age, progression rates among people with haemophilia were significantly slower, possibly because Kaposi's sarcoma was rare.

A Canadian analysis of causes of death in people with haemophilia between 1980 and 1995 showed that HIV attributable deaths (including co-infections) accounted for the majority (80-90%) in HIV positive patients. In contrast death due to haemorrhage was higher in both HIV positive and HIV negative patients.¹³⁷ Unlike non-haemophilia patients where cause of death was mainly opportunistic infection, cause of death in haemophilia patients was mainly intracranial haemorrhages and cirrhosis of liver.

Data from the UK showed that age at the time HIV seroconversion had a significant influence on survival rates amongst people with haemophilia, with longer

survival seen amongst those who seroconverted at younger ages. The age-gradient in survival was not explained by deaths expected in the absence of HIV infection or by confounding with other factors such as haemophilia type or severity.¹³⁸

An Italian study conducted a survival analysis among the cohort of HIV-positive people with haemophilia with AIDS at the Italian Haemophilia Registry. This study also showed that younger age at HIV seroconversion and at AIDS diagnosis were associated with a longer survival.¹³⁹ This study indicated an increasing survival from AIDS diagnosis to death over time, also as a result of the introduction of antiretroviral therapy. Survival trends were similar to those reported among homosexual men and intravenous drug users with AIDS, suggesting a similar access to the health-care system for individuals with AIDS.

In summary, the natural course of HIV/AIDS is similar with the exception of Kaposi sarcoma which is mostly found in men who have sex with men and is linked to coinfection with HHV8 infection (no KS cases have been observed in the Bonn Hemophilia cohort to date; n=420). In the Bonn cohort lowest survival rates were found for intravenous drug users most likely due to a higher risk for bacterial infections (endocarditis) and risk for overdose. The only HIV associated manifestation which may have an impact on an underlying bleeding disorder might be HIV-associated

thrombopenia. However, bleeding complications in this context have been very rare.

In the setting of HIV and hepatitis coinfection the risk for liver toxicity under HIV therapy is enhanced. This would also be true for IVDU with high risk for hepatitis coinfection. Overall, no difference has been found regarding time point of antiretroviral treatment initiation or choice of drugs depending on transmission risk. There have been a few reports of increased bleeding episodes under commonly used HIV first generation protease inhibitors which, however, were not observed in the Bonn HIV-infected haemophilia cohort with a preventive high dose clotting factor substitution policy.¹⁴⁰ Indeed, increased bleeding events have not been reported for any other HIV drug class.

There have been several case reports describing acquired F8 inhibitors in patients receiving interferon alpha for hepatitis C virus (HCV) treatment and in immune reconstitution inflammatory syndrome (IRIS) in patients being treated for human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS).¹⁴¹ While the potential impact of HCV or HIV drugs on triggering an inhibitor cannot be ruled out, the fact that this was only reported in case reports suggests a low incidence of these events. Therefore, in general there was no difference in treatment of HIV in individuals with a bleeding disorder with an inhibitor.

The UK Haemophilia Centre Doctors' Organisation (UKHCDO) manages the UK's national haemophilia database. The UKHCDO carried out a study on the impact of HIV on mortality rates of people with haemophilia between 1977 and 1999. Of 7,250 men with haemophilia, a majority of whom were also infected with hepatitis C, 1246 were HIV positive. During 1977-1984 annual mortality in severely haemophilic males was 0.9%. For those with HIV, annual mortality increased progressively from 1985 reaching over 10% during 1993-1996 before falling to 5% in 1997-1999, likely related to anti-retroviral treatment.¹⁴²

What advice and information would you expect a person to be given now about HIV, including advice and information about the risks of transmission, prognosis and treatment options? (Point 14.17 and Supplementary Questions 11 and 13)

Advice and information sharing in the context of HIV should be seen as an ongoing process rather than as a single event.

Information, explanations and advice being given to people diagnosed with or affected by HIV must be done with consideration of the complexity of the condition, existing treatments, transmission mechanisms and health literacy of the individuals concerned. Information may be given in a context where there is little detailed knowledge, pre-existing fear, and concerns about associated stigma and discrimination.¹⁴³

Testing for HIV is increasingly commonplace and more often being done on an 'opt-out' basis as part of other investigations in which blood testing is undertaken, or as sexual health screening in a primary care setting.¹⁴⁴ A reasonable knowledge base of any primary care

clinician is expected in order to facilitate initial discussion with a patient who is found to be positive for HIV. A suitable environment with adequate time given for such discussion is required. It would be unusual to expect a primary care clinician to give more than an initial diagnosis and brief explanation. This is mindful of both the potential shock of the diagnosis, and that only a very small portion of the information discussed may be retained beyond the diagnosis.¹⁴⁵

Most patients and families may consider looking online for further information, and signposting to authoritative NHS or third-sector resources should be considered and prepared.

Services that offer diagnostic testing for HIV should have an agreed pathway into specialist HIV care for people who are diagnosed HIV positive. People who have a new diagnosis of HIV should expect to have their HIV status fully assessed by appropriately trained staff within two weeks of receiving an HIV-positive test result. Those with a new diagnosis of HIV who have symptoms and/or signs potentially attributable to HIV (including those of primary infection) should be referred for urgent (within 24 hours) specialist assessment. People who receive an HIV-positive diagnosis as a hospital inpatient should expect to be reviewed by appropriately trained staff within 24 hours if their admission may be HIV related.¹⁴⁶

In a specialist HIV care setting, following full assessment, further details would be shared, and current level of understanding established, in a suitable, confidential environment. Adequate time for extensive, ongoing discussion over a number of clinic visits involving appropriate members of the multidisciplinary team should be planned.

Following initial clinical assessment and baseline investigations, a person with HIV should expect to have information about what HIV is and how it can affect their health and wellbeing. The person should be given information of the current stage of their HIV infection, including the CD4 count and viral load, any associated complications, their options for starting antiretroviral treatment and other associated interventions. This information should include choices of suitable drug combinations with risks and benefits. There should be clear understanding that HIV therapy is a treatment and not a cure, and requires long-term commitment and high levels of adherence. The arrangements for follow-up and monitoring should be outlined.

Information on prognosis will depend on the stage of infection. However, for the majority of people in the UK, newly diagnosed, asymptomatic and able to access treatment, life expectancy approximates to that of the general population. Information should be provided on how to maintain optimum health, including

advice on smoking cessation, recreational drug use, diet and exercise.

The implications of the diagnosis for others, particularly sexual partners and children, need to be explored with the patient thoroughly and sensitively.

How HIV can and cannot be transmitted to others should be discussed and reassurance provided that HIV is not transmitted via casual contact. The impact of effective treatment preventing sexual and vertical transmission should be explained.

Disclosure to others and support available from practitioners with skills in partner notification should be explored. This should be provided via sexual health services or within the HIV service by those with sufficient expertise.

People living with HIV should be offered written and verbal information, which is culturally and age appropriate, about prevention of HIV transmission, including mechanisms for partners to access pre- and post-exposure prophylaxis (PrEP and PEP) if relevant.

People living with HIV should be aware of the importance of avoiding future sexually transmitted infections to which they may be more susceptible and, if acquired, may make them more infectious to others in the context of sexual transmission of HIV.

People who have been diagnosed HIV positive should be made aware of the legal position in relation to HIV

transmission and how to protect themselves from prosecution. This should occur (and be documented) at the time of their initial diagnosis and subsequently as indicated.

Would you expect a person to be given any advice or information (and, if so, what) about starting a family? (Supplementary Question 11.1)

Desires and plans for parenthood should be discussed with all people living with HIV during initial assessment and revisited periodically during ongoing care and management. Women with HIV should be reassured that pregnancy will not adversely affect the progression of their HIV infection.

People with HIV should be aware that, with effective treatment and life expectancy near-equivalent to that of the general population, they can expect their children to reach adulthood and to become a grandparent.

People with HIV should be aware of the risks of vertical transmission of HIV to their baby (mother-to-child). For women who are on effective therapy and who avoid breastfeeding, the risk of vertical transmission is less than 1:1000. People with HIV should expect to have accurate information about their own risks of

vertical transmission during pregnancy, childbirth and breastfeeding, and how to minimise these risks. This will include the management of their pregnancy¹⁴⁷ and birth to reduce the risk of infection for the baby. The baby will need to be tested for HIV at birth and at regular intervals for up to two years. All patients benefit from pre-conceptual advice with regard to lifestyle choices and general health. This is particularly so if there is a pre-existing illness.

People with HIV should expect to have information about safe conception within a sero-different relationship, including pre-conception advice for themselves and their partners. People with an undetectable viral load cannot pass HIV to their sexual partners. The risk of vertical transmission rises if an HIV-negative woman acquires HIV during pregnancy or whilst breast feeding when viral load would be high. Information should be given about PrEP and PEP in this situation.

Women with HIV should expect to have information on how to feed their baby. In the UK, women with HIV are advised to avoid breastfeeding and to use replacement feeding. Women who elect to breastfeed their babies should be given specialist support and advice on how to manage this and the indications to stop breastfeeding.

People living with HIV should have access to accurate information and support for pregnancy choices,

including contraception and abortion. Information should be shared on the potential for interactions between oral contraceptives and ART to avoid contraception or ART failure.

People living with HIV who require investigation and treatment for infertility should be given information on ways to access fertility/conception services.

Would you expect a person to be given advice or information (and if so, what) about donating blood? (Supplementary Question 11.2)

HIV, hepatitis B and hepatitis C are blood-borne viruses and patients who have ever tested positive for these may not donate blood irrespective of whether they have been symptomatic or not.¹⁴⁸ All donated blood is routinely tested for hepatitis B, C and E as well as HIV.¹⁴⁹

What advice, information and support would you expect to be given to the family of a newly diagnosed person? (Supplementary Questions 11.2.2 and 13)

Implications of the diagnosis for family members, particularly for children and sexual partners, need first to be explored with the patient thoroughly and sensitively: working out with the patient to clarify who does and who does not need to be aware of the diagnosis, and then supporting the patient with sharing the information.

For family members who are aware of the diagnosis, an explanation of how HIV can and cannot be transmitted to others should be discussed and reassurance provided that HIV is not transmitted via casual contact. The impact of effective treatment on the longevity and wellbeing of people with HIV and its ability to prevent sexual and vertical transmission should be explained. Signposting to other reliable sources of information and support about HIV should be given (for example, NAM Aidsmap, Terence Higgins Trust, National Aids Trust).

All newly diagnosed HIV-positive patients attending adult HIV services should have any children identified, tested – or testing history obtained (and evidenced) –

and the information clearly documented. The risks of vertical transmission should be assessed and discussed. This should be handled sensitively and supportively with a partnership approach, bearing in mind that the health of the child/children, who may have acquired HIV, is a priority.

All children (defined as those who have not yet reached their 18th birthday) born to people living with HIV should be assessed for risks of vertical transmission. Testing children at risk of HIV acquisition should be discussed with at least one of the child's parents or legal guardians, and appropriate testing and follow-up organised with paediatric colleagues.¹⁴⁶

Sexual partners of people who test positive should receive a prompt offer and recommendation of an HIV test through partner notification procedures.

What support would you expect a newly diagnosed person to receive? (Supplementary Question 11.2.1)

The clinician-patient relationship is important at any time but particularly for patients with long-term conditions that have significant impact on the patient, their family, their relationships and their social world. People with HIV require professional care and peer support from trusted multidisciplinary teams to maintain support and continuity. People should be

assured of not just care but understanding, respect and excellence.

The GP and primary care team are likely to be involved with the initial presentation and diagnosis of illness, onward referral and support with the psychological and social aspects of care for the patient and their families. Throughout the course of the illness, this may include provision of information orally but may also include appropriate written material or signposting to relevant trusted websites or specific patient support groups and networks. It will include the management of test results, medication and referrals to community groups and secondary care. Everyone living with HIV should have access to appropriate peer support, ideally embedded within the clinical service and an integral part of the multidisciplinary team. Different learning and health literacy needs should be catered for, including the use of pictorial explanation and support and encouragement of patient self-recording,¹⁵⁰ which can increase understanding and retention of information.

Signposting and providing written information for a patient to consider after a more in-depth secondary care review is important given information retention issues, which are exacerbated if the patient is anxious during a consultation.

People with HIV should know how information about their diagnosis is shared among healthcare

professionals and be part of that decision. Sharing of information can cause anxiety and concern but is often critical for safe prescribing given the common interactions with drugs used to treat hepatitis¹⁵¹ and HIV.¹⁵² Of note, 91% of HIV patients, tested elsewhere, shared their HIV status with their registered GP.¹⁵³

Specialist HIV care is based on a multidisciplinary team model and often arranged in clinical networks. This means that a number of people and teams may be involved. While each may have specific roles in the management of the patient's care and treatment, they are also likely to have shared roles and responsibilities. Good communication between everyone involved is essential for best outcomes and if the patient is to have confidence in their care.

Living with HIV requires lifelong adjustments and management. With the drive towards personalised medicine and shared decision making, patients should be aware of the natural course of their condition, enabling them to seek advice and help when appropriate and to manage the impact of HIV and its complications on their daily lives. As with other long-term health conditions, people living with HIV should optimise self-management and access peer-support opportunities to promote their physical and mental health and overall well-being. Self-management approaches help people living with HIV gain confidence, skills and knowledge to manage their

own health resulting in improvements in quality of life and independence.

Clinicians should make no assumptions about patient preference to treatment and care options in HIV. Both Realistic Medicine¹⁵⁴ and NHS England¹⁵⁵ highlight the importance of effective shared decision making to achieve optimal patient care. It is important to listen to patient preferences and share decision making having ensured that the patient has the information needed to make an informed choice in an equal partnership.

BHIVA care standards recommend that people living with HIV should be actively involved in decisions about their own health and social care, and that people seeking care for HIV are participants in, not just beneficiaries of, health systems.¹⁴⁶ There should be active involvement of people who use services in the design, planning, delivery and review of those services. Active engagement in decision making may require support and resources for both people living with HIV and service providers. Service providers should be able to demonstrate their commitment to participation through identification of strategies, pathways and resources for both individual engagement in decision making and community engagement in service provision.

Please outline the work being undertaken to find a cure for HIV (Point 14.18)

HIV antiretroviral therapy (ART), when taken daily, is able to stop the replication of HIV (with undetectable viral load in the blood of an HIV positive patient).

Patients with undetectable virus do not transmit HIV to others and, in general, their immune system recovers over time. However, if treatment is stopped, detectable virus will return, usually within weeks. One of the great challenges for research is how to enable patients to stop therapy and remain with undetectable virus, free of the complications of infection. Cure may be 'sterilising', where there is no virus left in the body, or 'functional' where virus remains in the body but an individual does not require treatment.

The main challenges to developing a cure of HIV are as follows: (i) The virus is able to integrate itself into the DNA of infected cells. This is often referred to as 'latent' virus. This viral DNA remains as a reservoir, even if treatment is able to prevent the creation of new virus, and can re-emerge when treatment is stopped. (ii) These latently infected cells can expand in number even when a patient is on effective treatment. (iii) Although treatment may mean viral replication is not detectable in blood using standard tests, there can often be low-level production of virus which maintains the infection. (iv) Reservoirs of infected cells are found

in the cells of the immune system throughout the body, particularly in the tissue around the intestines, and are not therefore amenable to being removed. (v) Current HIV treatment, although lifelong, is generally well tolerated by most patients so new treatments need to be both highly effective and safe to be considered for widespread use.^{156, 157}

Current approaches

Bone marrow transplantation

The most high-profile approach to cure, with widespread media coverage, is bone marrow transplantation (BMT). The process of BMT involves using potent chemotherapy and irradiation to ablate an individual's immune system, removing the sites of viral reservoirs. Stem cells from a different patient 'allogenic' are then infused to restore the immune system. In the setting of HIV infection, stem cells are chosen from a donor with a particular naturally occurring genetic type, known as 'CCR5 delta32 deletion homozygotes'. This genetic type is relatively rare. Individuals who carry two copies of the delta32 deletion are resistant to HIV infection.

BMT using this approach has been able to cure only a very small number of patients. It is not suitable for widespread use in HIV cure, primarily because the risks of the procedure are high (particularly related to toxicity of drugs and vulnerability to infection) and

cannot be justified for patients who are healthy on their medication. In addition, individuals with the appropriate genotype are relatively uncommon in the population (approximately 1%). The procedure has thus far only been used for six individuals who have a life-threatening condition (other than HIV) that require the procedure. To date, two/three have achieved what is thought to be a sterilizing cure.⁶⁴

There is ongoing research to develop milder forms of the procedures that could be suitable for more widespread use. BMT using a patient's own cells requires less intensive chemotherapy and there are studies ongoing exploring the potential for using gene editing techniques to stop CCR5 gene expression in an infected individual's cells. Tools such as zinc-finger nucleases and CRISPR/Cas9 editing offer promise, but are not yet sufficiently well developed to offer routinely.

Strengthening the immune response to HIV

Therapeutic vaccination

Progress in the development of an HIV vaccine that can prevent infection has been disappointing to date, but the approaches taken to enhance the body's specific immune response to HIV are being explored in HIV cure therapy. In combination with other agents (see below), there have been clinical studies suggesting that a vaccine producing strong T

cell responses may help control virus, though falling short of functional cure. Ongoing work is focused on developing stronger immune responses that can recognise the broad range of viral targets present during a natural infection.

Broadly neutralising antibodies (bNAbs)

Clinical studies have started investigating antibodies that have been selected to neutralise a wide range of viral strains. When given as an infusion, they may help clear free virus from a patient's blood and potentially clear HIV-infected cells. The initial hope is that periodic infusion of antibodies may be able to control HIV sufficiently for patients to stop their daily HIV treatment, although it is likely that combinations of antibodies will be needed to prevent viral resistance. Work is ongoing to engineer new antibody-like molecules that can target a wider range of viral targets.

Engineered cell therapy

Treatment with cell-based therapies have transformed cancer care in recent years and are being evaluated for a role in HIV cure. Known as 'CAR-T therapy' ('chimeric antigen receptor – T cell'), T cells from a person's own immune system are removed and modified to include molecules that target a specific cell type (for example, lymphoma or HIV infection), before being given back to patients. In the case of HIV, the molecules included may be based on fragments of

broadly neutralising antibodies (bNAbs, see above) specific for HIV. Other cell types (for example, iNKT cells) are being investigated that might allow ‘off the shelf’ treatments. Work in the area of cellular therapy for HIV cure is in its early stages.

Activation of infected HIV cells, latency reversal agents

The approach of ‘kick-and-kill’ is exploring the likely scenario that successful cure based on strengthening the immune system’s response to HIV-infected cells is likely to first require activation of latently infected cells so they can be recognised. A range of drugs (known as ‘latency reversal agents’ [LRAs]) is being studied including HDAC inhibitors (for example, romidespin, vorinostat), toll-like receptor agonists (for example, vesatolimod) and disulfiram. The first randomised trial for HIV cure therapy, RIVER, was completed in 2019, but found no evidence of reduction in reservoirs of HIV from a combination of LRA (vorinostat) and therapeutic vaccination.¹⁵⁸

Modify the HIV positive patient's immune system

Inflammation as a result of HIV infection is associated with a range of health impacts including cardiovascular disease and malignancy. Drugs that reduce inflammation and weaken immune responses (for example, sirolimus) have been associated with

reducing HIV reservoirs in small studies and are being actively investigated.

Summary

The understanding of how HIV causes long-term infection continues to deepen, and in doing so provides new opportunities for potential cure. However, none of the above approaches has shown sufficient promise to be available for widespread clinical use in the next 10 years. A combination of approaches is likely to be needed to effect a cure. With over 80% of those infected with HIV living in sub-Saharan Africa, most healthcare systems will have insufficient resources to deliver a complex medical intervention at scale. Consideration needs to be given to prioritising therapies that can be delivered in resource-limited settings.

Supplementary questions not addressed above

S 14. What is the current optimum model of care for a person diagnosed with HIV and/or AIDS? Please ensure that you include:

14.1. palliative care;

14.2. how the care of co-infected people should be managed and coordinated.

To be answered in the Supplementary Report

S 15. To the extent that HIV and/or treatment for HIV causes or is linked to other health conditions (such as bleeding disorders) and secondary complications, to what extent should care for HIV and those conditions be co-ordinated, and what is current best practice and the optimum clinical model in this regard?

To be answered in the Supplementary Report

S 18. Following successful treatment for HIV such that a person has an undetectable viral load, what follow-up scans, blood tests and/or checks and treatment should the person receive, how often and over what period of time?

To be answered in the Supplementary Report

S 19. What are the current clinical guidelines for infection control when treating a person with HIV?

The general principle of infection control when treating all patients including those with HIV is one of 'standard precautions' for all patient care. Standard precautions are the minimum infection prevention practices that apply in any setting where healthcare is delivered, regardless of suspected or confirmed infection status of the patient. Standard precautions are designed to reduce the risk of transmission of blood-borne and other pathogens to healthcare workers and other patients from both recognised and unrecognised sources.

Standard precautions include the following

- (1) Hand hygiene.
- (2) Use of personal protective equipment (for example, gloves, masks, eyewear) to protect the healthcare

worker (HCW) from exposure to potentially infectious agents. This needs to be appropriate for the type of patient interaction – for example, use of mouth, nose and eye protection during procedures that are likely to generate splashes or sprays of blood or other body fluids.

- (3) Respiratory hygiene/cough etiquette.
- (4) Prevention of needlestick and injuries from other sharp instruments (engineering and work practice controls). Healthcare settings should have robust processes for the reporting of and follow-up of needlestick, sharps and splash injuries.
- (5) Safe injection practices (that is, aseptic technique for parenteral medications).
- (6) Provision of sterile instruments and devices.
- (7) Clean and disinfected environmental surfaces, and patient care equipment.
- (8) Safe handling of linen. Guidance on procedures for chemical disinfection of infected linen are provided.¹⁵⁹
- (9) Safe waste disposal, and local code of practice for dealing with spillages and other forms of contamination.

If admitted to hospital, HIV-positive patients do not need to be isolated in a single room unless they are suspected of having another condition which may be

transmissible to others via the airborne route – for example, tuberculosis.

Immunisation of healthcare workers

There are currently no vaccines available against HIV, although policies and procedures for the reporting of needlestick and splash injuries will ensure that a risk assessment takes place and, if HCWs are exposed to HIV post-exposure, anti-viral prophylaxis will be provided.

Procedures for taking blood specimens and laboratory handling of samples related to treatment of patients with HIV

The Health and Safety Executive (HSE) provides guidance for procedures for taking blood specimens and for clinical laboratories handling samples from patients with HIV in the course of their treatment.¹⁶⁰ This includes the use of standard precautions for all patients, as all blood samples should be considered potentially infectious. Therefore, gloves should be worn when taking blood for all patients. ‘Danger of infection’ labels should be used for samples known to pose a risk to staff handling the sample.

Renal dialysis units

In 1972, the Rosenheim Advisory Group issued good practice guidelines to prevent the transmission of hepatitis B in renal dialysis and transplant units. Since

then, with the identification of both HIV and HCV, new guidance 'Good practice guidelines for renal dialysis/transplantation units and the prevention of and control of blood-borne virus (BBV) infection', was published in 2002 and remains current.¹⁶¹ Patients with HBV should ideally be dialysed in separate isolation facilities. Where these are not currently available, patients should be segregated in a separate area from other patients during dialysis. Patients with HCV should also be segregated from uninfected patients during dialysis. Segregation of patients with HIV should be considered, based on a local risk assessment. Because of the risk of cross-infection, patients with different BBV infections should not be dialysed in a single segregated area at the same time.

Separate dedicated dialysis machines should be used for patients with HBV. Dedicated machines are not required for patients with HCV or HIV provided that cleaning and disinfection processes are properly carried out between patients according to the manufacturers' instructions. Whenever possible, staff should nurse only infected or uninfected patients during a shift. If this is not practicable, more experienced staff should be assigned the task of caring for a mixed group of patients.

Handling the deceased

Whenever blood or body fluid is present, there is a potential risk of blood-borne transmission and

appropriate protective measures should be taken. Only leakage of blood or body fluids produces a risk of BBV infection, and simple hygiene measures are adequate to prevent transmission. However, whilst hygienic preparation is acceptable, current HSE guidance stipulates that bodies with BBV infections can only be embalmed if additional transmission-based precautions are in place with appropriate robust measures for the use of sharps (for example, minimise use or use safer sharps devices) as this presents significant risk of exposure to workers.¹⁶²

Fertility treatment

Centres providing facilities for the processing and storage of gametes and embryos for use in fertility treatments must carry out testing for hepatitis B, hepatitis C and HIV, and devise a system for storage which clearly separates gametes and embryos from individuals who have tested positive from those who have tested negative.¹⁶³

S 20. What, if any, reporting and/or data collection methods are used to record secondary health conditions or complications which may have arisen from HIV/AIDS and/or any treatment received for the same?

To be answered in the Supplementary Report

S 23. What training is currently given to medical students and medical professionals who work outside the field of infectious diseases, about HIV and AIDS?

To be answered in the Supplementary Report

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Verifying statements

Each contributing group member confirms that he or she understands his or her duty to provide independent evidence and has complied with that duty.

All contributing group members confirm that in respect of those parts of the report to which they have contributed:

- (i) They have made clear which facts and matters referred to in this report are within their knowledge and which are not.
- (ii) Those that are within their knowledge they confirm to be true.
- (iii) The opinions they have expressed represent their true and complete professional opinions on the matters to which they refer.

Authors

Professor Jane Anderson

Jane Anderson is chair of the National AIDS Trust and a past chair of the British HIV Association. She is a consultant physician in HIV medicine at Homerton University Hospital NHS Foundation Trust. She chairs the Public Health England Advisory Group for HIV and Sexual/Reproductive Health and she represents London clinicians in the NHS England Clinical Reference Group for HIV. She has worked as a clinician and researcher in HIV medicine since the virus emerged in the 1980s. She holds honorary academic appointments at St Bartholomew's Hospital, The London School of Medicine and Dentistry and University College London. Her work focuses on ethnic minority and migrant populations in relation to HIV in the UK, with a particular focus on HIV care for women and families. Her wide-ranging work engages with the current medical, social, ethical and legal challenges posed by HIV. She is also a visiting fellow at The King's Fund, an independent charity working to improve health and care in England.

Professor Graham Cooke

Graham Cooke is a National Institute for Health Research (NIHR) Research Professor of Infectious Diseases at Imperial College London, Honorary Consultant and Lead for co-infection services within

Imperial College NHS Trust. Previously, he was based at the Africa Health Research Institute in KwaZulu-Natal. He led the Commission on Accelerating the Elimination of Viral Hepatitis published in 2019, chairs the WHO Committee on the Selection and Use of Essential Medicines and is a member of the National Viral Hepatitis Strategy Group. He chairs the British HIV Association (BHIVA) Hepatitis Expert Advisory Group which is leading efforts for the microelimination of hepatitis C in those living with HIV. His current work focuses on precision medicine for managing infectious diseases and access to medicines, particularly for HIV/viral hepatitis. He led the clinical workstream for the MRC Stratified Medicine Consortium (STOPHCV) from 2003-19, and is infection lead for the London In-vitro diagnostics cooperative. He was chief investigator on the STOPHCV-1 trial and currently has studies running in the UK and Vietnam, in collaboration with the MRC Clinical Trials Unit.

Professor Philippa Easterbrook

Philippa Easterbrook is Senior Scientist in the Global Hepatitis Programme, HIV department at the WHO (World Health Organisation) Headquarters in Geneva. She is an HIV and infectious diseases physician and epidemiologist who has worked in the UK, United States and Sub-Saharan Africa. At WHO, she has led the development and dissemination of global normative guidance for HIV as well as Hepatitis B and C testing

and treatment. She also provides technical guidance to national programmes worldwide on the implementation of hepatitis B and C testing and treatment scale-up programmes as part of a global elimination strategy. For eleven years, she was Head of Department, Professor of HIV Medicine, and consultant physician in Infectious Diseases at King's College London, and also Head of Research at the Infectious Diseases Institute in Uganda. Philippa has served as a Member of the UK Medical Research Council Infection and Immunity Committee, and was vice-chair of the World Health Organization Guidelines Review Committee. Her HIV research has encompassed epidemiology, clinical trials, operational and qualitative research, and laboratory-based studies.

Sian Edwards

Sian Edwards has worked as a nurse in HIV care for 32 years. Her experience includes both HIV clinical nursing and educational roles in HIV units in the UK, Australia and Zambia. She initially worked as an HIV community nurse in Sydney, Australia in 1986, a specialist lecturer in HIV and AIDS at St. Thomas' Hospital London and as a nurse lecturer at Chelsea and Westminster Hospital. Following two years working in Ndola, Zambia, in a Home-Based Care Program she returned to the UK as a community clinical nurse specialist in the Guy's and St Thomas' Haemophilia Reference Centre. Sian managed two research

projects while a senior lecturer in HIV and Sexual Health at Brighton University, focusing on recording the life histories of people with haemophilia and HIV and their families. She has written on the topic of HIV care in nursing and management of AIDS, including a set of guidelines for healthcare workers in 1994. She is currently employed as an HIV Research Nurse Coordinator at Northside Clinic in Melbourne, and has just completed the life history project 'The AIDS Era: an oral history of UK healthcare workers.'

Professor David Goldberg

Professor David Goldberg is a consultant in Public Health Medicine and Clinical Epidemiology at Health Protection Scotland (HPS) who, over the last 25 years, has developed, implemented and evaluated interventions and monitoring techniques to prevent HIV and hepatitis B and C infections and their diseases, both nationally and internationally. He led the team which developed and coordinated the implementation of Scotland's Hepatitis C Action Plan. Previous roles include Henry Mechan Professor of Public Health, Deputy Director of Health Protection; and former Acting Director of the Scottish Centre for Infection and Environmental Health. He is an honorary professor of Public Health at the University of Glasgow and a professor of Public Health at Glasgow Caledonian University. He serves on several Scottish committees and is involved in the postgraduate supervision and

teaching of students affiliated to the University of Glasgow, and is the author of approximately 250 peer-reviewed articles. He currently chairs Scotland's Hepatitis C Treatment and Therapies Group.

Dr Katie Hands

Dr Katie Hands is a Consultant Haematologist with the Scottish National Blood Transfusion Service (SNBTS) and is based at Ninewells Hospital in Dundee. She studied medicine at the University of Dundee, and during haematology specialty training undertook a PhD under the supervision of Professor Ron Hay. Dr Hands was appointed as a Consultant with SNBTS in 2016, providing transfusion medicine support for NHS Tayside, where her role includes promoting the safe and appropriate use of blood in all hospital departments. Her wider roles within SNBTS include policy development and transfusion medicine teaching as part of a National teaching programme for haematology registrars. She is a member of the British Society for Haematology Transfusion Task Force, and is involved in the preparation of evidenced based guidelines relating to all aspects of blood transfusion in the UK.

Dr Scott Jamieson

Dr Scott Jamieson is a General Practitioner in Kirriemuir, Scotland. He sits on the Royal College of General Practitioners (RCGP) Scottish Council, where

he is the Executive Officer for Quality Improvement. He is Clinical Prescribing Lead for Angus Health and Social Care Partnership, sitting on the local Drug and Therapeutics Committee and the Non-Medicines Advisory Group. In addition to this, he is a GP trainer and GP representative on the Scottish Intercollegiate Guidelines Network (SIGN) Council, an organisation dedicated to improving the quality of health care for patients in Scotland by reducing variation in practice and outcome, through development and dissemination of national clinical guidelines. His interests include dermatology, minor surgery, and sexual and reproductive health.

Dr Katie Jeffery

Katie Jeffery is a consultant in Clinical Infection, the Infection Control Doctor (ICD) and Director of Infection Prevention and Control (DIPC) at the Oxford University Hospitals (OUH) NHS Foundation Trust. She trained in Microbiology with a particular interest in Virology, and has a PhD in HTLV-1 infection. Her clinical interests are infection prevention and control, viral diagnostics, viral hepatitis, and infections in the immunocompromised host. Previously she was Clinical Lead for Microbiology in the OUH, where she led on the introduction of a number of new laboratory assays in serology and molecular diagnostics. She holds a number of positions of responsibility both locally and nationally, including being a Virology Examiner for

the Royal College of Pathologists, the Vice President of the British Infection Association, and a member of the Expert Advisory Group for Infectious Diseases for the MHRA (Medicines and Healthcare products Regulatory Agency). She has nearly 20 years' experience in treating patients with viral hepatitis, and is regularly involved as an investigator in national and international studies, especially those that benefit NHS patients by allowing early access to new drugs for the treatment of hepatitis C.

Dr David Johnston

David J Johnston OBE is a General Practitioner at Maine Medical Practice in County Antrim. He is a Clinical Director of Dalriada Urgent Care, an out of hours primary care provider for the north east of Northern Ireland . He is also a member of "Practice 400" which provides care for General Medical Service designated "violent patients" and was involved in the establishment of ECHO, a scheme to enhance primary care services for homeless patients. His interest areas include pre-hospital immediate medical care, out of hours primary care and rural medicine. He has been a GlaxoWellcome research fellow with the University of Ulster and was involved in researching rural General Practice in Northern Ireland. David served as chairman of the NI Council of the Royal College of General Practitioners (RCGP) from 2008 to 2011 and was also

a member of the UK council of RCGP. He continues to chair a number of community charities.

Professor Jürgen Rockstroh

Jürgen Rockstroh is Professor of Medicine and Head of the HIV Outpatient Clinic at the University of Bonn, Germany, which treats the world's largest cohort of HIV-infected haemophiliacs. In addition to his clinical practice, Dr Rockstroh is involved in HIV research on: antiviral therapy, including new drug classes; the course of HIV disease in haemophiliacs; and HIV and hepatitis co-infection. He has been an investigator in multiple clinical trials of antiretroviral agents and treatments for HIV and hepatitis co-infection. He was the president of the German AIDS Society from 2007 to 2011, has been an executive committee member of the European AIDS Clinical Society (EACS) since 2009 and in 2019 was elected as president of EACS. Dr Rockstroh has been a member of the governing council of the International AIDS Society since 2011, and currently chairs the hepatitis research activities in NEAT (European AIDS treatment Network) and EuroSIDA. Between 2011 and 2017 he chaired the National German AIDS Advisory Panel, and the EACS co-infection guidelines. Dr Rockstroh has authored and co-authored over 500 publications in peer-reviewed journals, and over 70 book chapters. The German Society for Infectious Diseases awarded Dr Rockstroh the national AIDS research prize in 2005.

Dr Mallika Sekhar

Dr Mallika Sekhar is a consultant haematologist and honorary senior lecturer at UCL. She specialises in myeloproliferative diseases and blood transfusion, across the University College London Hospital and Royal Free Hospitals, with a special interest in patients with vascular thrombosis and myeloproliferative diseases. She has been involved with writing Management Process Description (MPD) guidelines for the British Committee for the Standards in Haematology (BCSH). Dr Sekhar has been the Lead Investigator in studies on abdominal vein thrombosis in myeloproliferative diseases and transfusion in haematological malignancies, and a member of the National Cancer Research Institute (NCRI) MPD and supportive care clinical studies group. She was a member of the clinical expert panel on the Pathology Modernisation initiative for London, and is the lead for undergraduate education in haematology at the Royal Free campus. Previously, she was chair of the London Regional Council of the Royal College of Pathologists and has been a member of the National Blood Transfusion Committee Group on Education since 2012.

Professor Gareth Tudor-Williams

Professor Gareth Tudor-Williams is Professor of Paediatric Infectious Diseases at Imperial College London, and Consultant in Paediatric Infectious

Diseases at Imperial College Healthcare NHS Trust, St. Mary's Hospital, London. His interest in paediatric infectious diseases was sparked after having worked for two years in the Himalayas for Save the Children Fund UK. He has spent 30 years contributing to some of the incremental improvements in the management of children living with HIV, and the prevention of vertical transmission from mothers to their infants. He is a Fellow at Duke University, North Carolina and a Visiting Scientist at the National Institutes of Health (NIH), Bethesda, Maryland. During his career, he has worked with the World Health Organisation (WHO) and UNICEF in the Northwest Sindh Province of Pakistan. Since 1994, he has helped run a multi-disciplinary service for children infected with HIV, young people and their families at St. Mary's Hospital. He was the founding chair of the Children's HIV Association of the UK and Ireland (CHIVA), alongside being a passionate undergraduate and postgraduate educator, for which he received the IC School of Medicine's Distinguished Teacher Award in 2017.

Dr Jonathan Wallis

Dr Jonathan Wallis is a consultant haematologist. He has a keen interest in transfusion, and his publications include studies on leucodepletion and infection; transfusion-related acute lung injury (TRALI); long term survival after transfusion; and the 'Tag and Label' system for blood administration. Dr Wallis is an

active member of regional and national transfusion committees, including having chaired the British Blood Transfusion Society (BBTS) Hospital Transfusion Special Interest Group. He also chaired the BBTS Scientific Meetings Administration Committee, and the International Society of Blood Transfusion (ISBT) Working Group on Clinical Transfusion. He initiated and runs the Newcastle course for Transfusion Practitioners and Biomedical Scientists on alternate years, and is also the Associate Editor of Transfusion Medicine.

Dr Ian Williams

Dr Ian Williams is a senior clinical academic in the Centre for Clinical Research in Infection and Sexual Health Institute for Global Health at University College London, and an honorary consultant physician at Central North West London NHS Trust and University College Hospitals NHS Trust. He has extensive clinical and research experience in HIV medicine. He has been involved with all aspects of care of HIV positive patients since 1987. His main research interests are antiretroviral therapy, HIV associated co-morbidities and primary HIV infection. He was chair of the British HIV Association (BHIVA) from 2008 to 2011 and has been a panel member of several national and international clinical guideline committees including chair of the BHIVA Antiretroviral Treatment (ART) guidelines in 2012. He was chair of the Clinical

Reference Group for HIV (an expert advisory group) for NHS England from 2015 to 2019.

