Xplore Health

DISCOVER THE LATEST ON HEALTH RESEARCH

Educators' guide "Towards AIDS eradication"

(Background information)

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1. Introduction

These teacher guidelines will give you information on the Xplore Health module “Towards AIDS eradication”. It will first introduce the topic to enable you to prepare your lesson using the different multimedia tools that you will find on the website. The guidelines provide information on the state of the art in this research field and on the ethical, legal and social aspects surrounding this topic.

2. State of the art

2.1. Introduction/Epidemiology

HIV stands for ‘human immunodeficiency virus’. At the moment, around 33.3 million people in the world are infected with HIV and 7000 new infections are diagnosed every day.

HIV is a member of the retrovirus family. These viruses live by inserting a copy of their own genome into the DNA in our cells. They are then treated like our own genes and use the machinery of our cells to make new viruses. These new viruses can then infect other cells.

HIV specifically infects the cells of the immune system that we use to destroy infections – mainly CD4+ T cells and macrophages. Infection of these cells impairs or destroys their ability to function normally. This leads to immune deficiency and infected people are more susceptible to a wide range of so called opportunistic infections that the immune system would normally be able to overcome.

Once an HIV infected person develops several symptoms linked to immunodeficiency, their illness is called AIDS, which stands for ‘acquired immunodeficiency syndrome’. Most untreated people with HIV eventually develop AIDS, and usually die from opportunistic infections or cancers that occur when the immune system is weakened. Since its discovery in 1981, more than 30 million people have died from AIDS, with the majority in sub-Saharan Africa and a growing number in South and South East Asia.

2.2. Transmission

There are three main transmission routes for HIV:

- sexual
- blood-borne

- mother-to-child

Sexual transmission

The majority of infection is spread through unprotected sexual intercourse. This occurs when virus-containing secretions from the infected person come into contact with genital, oral or rectal mucous membranes of the uninfected partner. Transmission during sexual relations accounts for almost 90% of total infections in the UK, and this is split fairly evenly between those participating in heterosexual sex or sex between men.

Blood-borne transmission

Blood-borne transmission accounts for infection of intravenous (IV) drug users, haemophiliacs and recipients of blood transfusions and can occur when infected blood is directly transferred from one person to another or comes into contact with an open wound. Incidences of transmission via blood products in healthcare situations in the developed world are rare as all blood is screened for HIV before treatment. Infection through IV drug use is still relatively common (5% in the UK) due to the reuse of needles among injecting drug addicts. This type of infection is significantly more common in Eastern Europe (44%)

Mother-to-child transmission

Vertical or 'mother-to-child' transmission can occur during pregnancy, childbirth or via breast feeding. In the developed world, transmission via this route is normally prevented by treating the mother with antiretroviral drugs and performing a Caesarean section during birth. In developing countries however, up to one in three babies born to infected mothers will contract HIV (this makes up to 19% of all new infections).

2.3. Stages of disease

There are three stages of infection recognised in patients infected with HIV. In the first few weeks following exposure to the virus, massive viral replication takes place resulting in high virus levels in the blood. Within weeks of this initial infection, viral replication drops greatly because the immune response to HIV is strong. Then the infected person goes through a stage with no symptoms, which is known as clinical latency. During this time, the number of an important cell type in the immune system, called CD4+ T cells, decreases steadily so that by the time symptoms are noticed, the individual has less than 300 CD4+ T cells/µl (an uninfected person has 500-1000 CD4+ T cells/µl). At the same time, there is an increasing

level of virus in the blood and lymph nodes and this is the beginning of the third, or symptomatic phase, which includes the progression to AIDS.

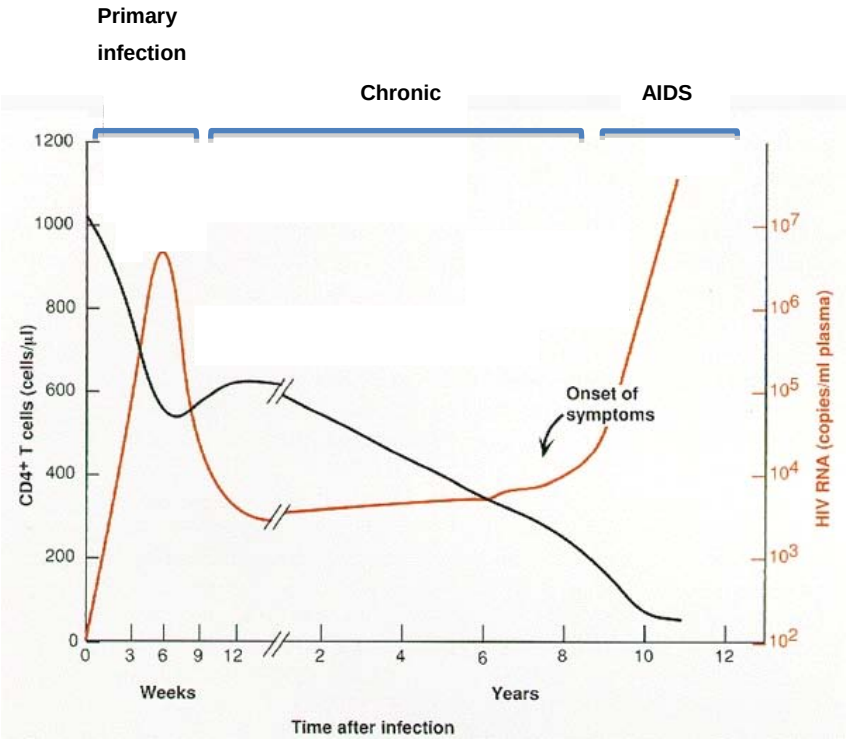

Fig. 1. The disease course of HIV infection. Amount of CD4+ T cells (black) and level of virus in the blood (red) is shown

Initial Infection: Acute Seroconversion Syndrome

For many people, initial infection with HIV may be asymptomatic, but as many as 40-90% of patients in the early stages of HIV infection develop an acute glandular fever-like infection after approximately two to six weeks following exposure. They will often experience fever, rash, joint pains and enlarged lymph nodes.

Seroconversion refers to the development of antibodies to HIV and usually begins between 1 and 12 weeks following infection. The production of these first antibodies is slow, and when they appear, they have only a weak ability to kill the virus. The initial burst of HIV replication is mostly contained by the actions of another cell in the immune system called a CD8+ T cell. The action of the immune response during the early stage of infection is fairly successful, and able to cause a large decrease in the amount of virus in the blood (called a patient's viral load (VL)). However it is not able to stop it completely and HIV replication still occurs in lymph nodes.

Whether or not symptoms are noticed during this period, the high levels of virus in the blood means that individuals are particularly infectious.

Chronic Infection: Clinical Latency

After initial infection, most patients have a period of 'clinical latency' that may last for years. Freedom from symptoms does not mean there is no viral replication. The level of infectious virus in the blood during this time is low and maybe even undetectable. Throughout clinical latency the immune system is gradually getting weaker, in particular, there is an overall loss of CD4+ T cells. As the immune system becomes less effective, the patient is more likely to be infected by other organisms. Once this happens, the doctor will diagnose AIDS.

AIDS

A person is classed as having AIDS when the number of their CD4+ T cells falls below 200/µl of blood and they have at least one of 20 opportunistic infections or HIV-related cancers. The destruction of cell-mediated immune responses means that infection by common, usually harmless environmental organisms (eg. Pneumocystis jirovecii) can be life-threatening. Later in infection, the reactivation of herpesviruses can also cause severe recurrences of shingles, Epstein-Barr virus-induced B-cell lymphomas or Kaposi's sarcoma.

The length of time taken for an HIV infected individual to progress to AIDS varies significantly, and depends on many viral, host and environmental factors. Without treatment, most infected people will be diagnosed with AIDS within 5-10 years. However, since the introduction of antiretroviral therapy (ART) in 1996, the number of people in developed nations that become sick from diseases linked to AIDS has reduced. In the UK, there have been approximately 27,000 diagnoses of AIDS since the beginning of the epidemic in 1981, and almost 20,000 people have died.

2.4. Prevention

An extremely important part of the treatment of HIV infection is prevention. HIV is a very fragile virus and cannot survive for long outside the cell. Transmission by the three modes described above can be readily prevented with appropriate precautions.

New preventive technologies such as microbicides (gels, creams or sprays capable of killing the virus) are continually being tested for their ability to prevent transmission through sexual exposure to HIV. At the moment though, condoms are still the main focus of prevention strategies for HIV and other sexually transmitted infections.

The screening of blood and blood products before treatment and the use of disposable syringes are the most effective ways of reducing infection through contaminated blood.

Infection rates among children born to mothers living with HIV have declined by 26% from 2001 to 2009, due mostly to drugs and the ability of infected mothers to give birth by Caesarean section, along with alternatives to breast feeding for infants.

2.5. Treatment

There is currently no cure for HIV.

At the moment, the only treatment options available are a combination of antiretroviral drugs which act at different steps in the life cycle of HIV. Current antiretrovirals target the following stages of HIV replication (see Fig. 2.):

1) Attachment/Fusion
    - This is the newest class of drugs and it interferes with the binding, fusion or entry of the HIV virus into the cell, either by changing a part of the outside of the virus or blocking the parts of the cell membrane that the virus would normally bind to.
2) Reverse transcription
    - These drugs were the first to be developed and act against the viral reverse transcriptase (RT) enzyme. They work either by physically binding to and inhibiting the enzyme's activity or interfering with the production of new viral DNA by forcing it to stop before it is finished.

3) Integration
    - Drugs that act on the viral enzyme integrase prevent the virus from inserting its genome into the DNA of the cell. This means that no new viruses can be produced.
4) Maturation
    - Inhibitors that stop the function of the viral enzyme protease only let non-infectious viruses be produced.

HIV multiplies at a very fast rate, and is able to change itself to become resistant to any drug that it comes across. Using these drugs in a combination of at least 3 different types at once makes it harder for the virus to adapt and become resistant, as it then needs to make multiple changes which may make it less able to infect. So for patients who stick carefully to

their treatment regime, combination ART means that there should be a longer period of time before the virus can become resistant to the drugs, and therefore the virus levels in their blood may be undetectable for many years. For these patients, progression to AIDS is slowed down and a newly diagnosed patient on ART can now experience an improved quality of life with an average life expectancy of 20-50 years depending on the age at which they were infected.

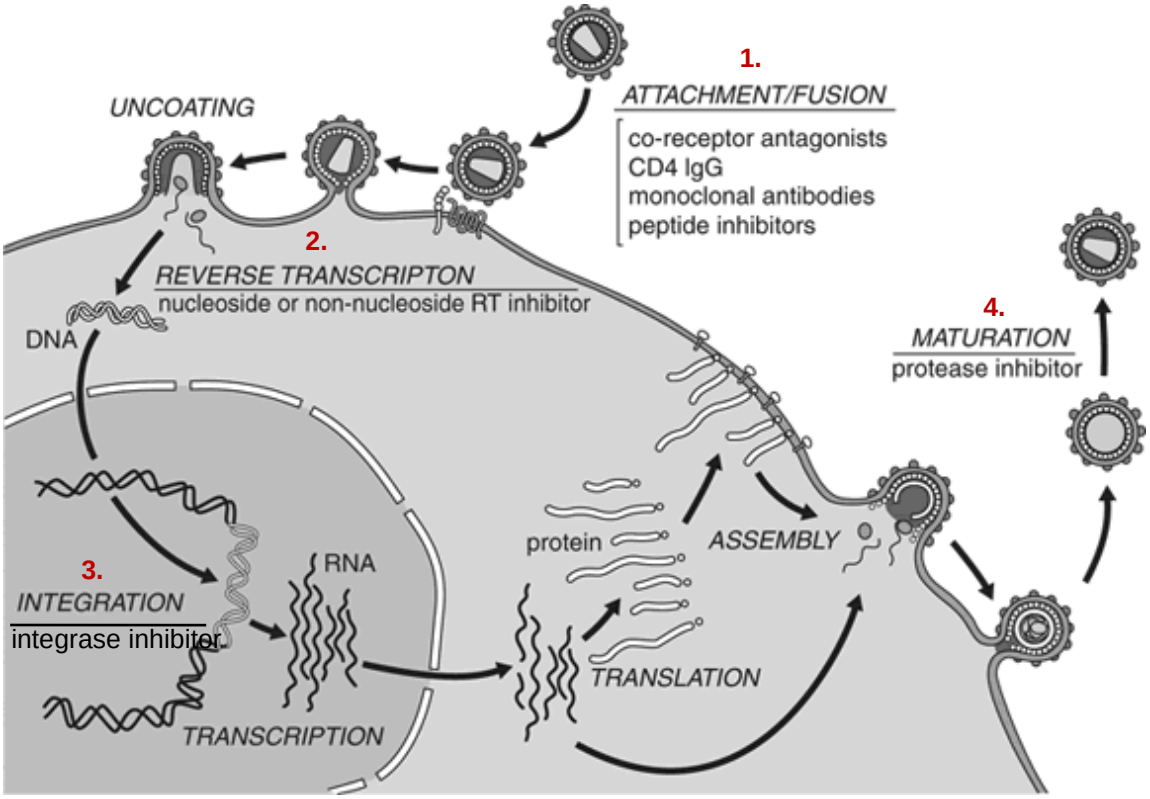

Fig. 2. The life cycle of HIV, showing the stages targeted by antiretroviral drugs.

So why don't drugs eliminate HIV from the body?

Early on, the success of combination ART in reducing HIV replication to undetectable levels led many to believe that a cure for HIV infection had been found. However in reality it seems there are at least three major barriers to curing HIV.

- Long-lived latently infected cells
    - These are infected cells in which the virus is silent, replicating only occasionally and at low levels. These cells can persist for long periods of time and are unaffected by ART or host immune responses.

- Anatomical reservoirs
    - This refers to cells in locations that are physically protected from the effect of ART (eg. virus in brain cells escape from drugs that can not cross the blood-brain barrier).
- Residual viral replication
    - This is due to the inability of ART to 100% inhibit the virus, which results in a continuous low level of replication.

A cure for HIV

There are two possible ways of achieving a cure for HIV.

- Sterilising cure

This refers to a situation where HIV is treated and then disappears altogether. This would mean that all infected cells were eliminated and the patient would have a VL of less than one virus/ml.

- Elimination of HIV following bone marrow transplantation

The only example of this type of cure is the recent report of a patient from Berlin with acute myeloid leukaemia (a cancer of white blood cells) who received a bone marrow transplant from a donor who had a deletion in the CCR5 gene (a human cell needs to have CCR5 on its surface before it can be infected with HIV). After the transplantation, this patient stopped taking ART and has had a VL of less than one virus copy/ml of blood for the three years. Bone marrow transplantation may not be a realistic cure for everybody with HIV infection, but understanding how this patient's 'new' immune system was able to respond positively and completely against infection will be useful in developing treatments available to everyone.

Making cells resistant to HIV

These studies aim to copy the elimination of virus that was seen in the Berlin patient after bone marrow transplantation. He was transplanted with bone marrow cells from a person who had a genetic trait (CCR5 gene deletion) that protects some people from HIV infection. In one example, patients had their own T cells removed which were then treated so that the CCR5 protein (which assists in HIV entry into cells) no longer worked in these cells. These cells were then put back into the patient and the researchers saw that the cells were able to carry out their usual functions for many months. While clinical use of this method of treatment

is many years away, the results show that we may one day be able to change any cells in an individual to be better able to eliminate the virus.

Functional cure

This alternative approach is similar to the idea of 'remission' in cancer patients, where a patient has long term good health without treatment, in the best case with a VL of less than 50 virus copies/ml of blood.

Elite controllers

Elite controllers are a unique group of HIV infected patients who do not have any symptoms and do not need to take drugs to keep their blood VL at an undetectable level. Multiple studies have looked at ways an elite controller's genetic makeup, infecting virus strain and immune response could be interacting to allow them to stay so healthy. In many cases, it seems that a set of genes responsible for alerting the immune system to which cells in the body are infected (called MHC class I) is linked with an elite controller's ability to naturally control of HIV infection. Several components of the immune system, such as a type of T cell called 'natural killer' (NK) cells that are able to kill virus infected cells, also seem to be more active in many of these patients.

2.6. Future strategies for elimination HIV

Several options to eliminate any virus that remains after a patient has been using ART are currently being investigated.

Treatment intensification

This involves changing a patient's drug regime to include drugs from more categories than they would normally be prescribed. The results from these studies so far have been disappointing, and no increased destruction of virus is seen.

Early treatment

In these studies, patients are given ART before their CD4+ T cell counts fall below 200/µl in the hope that less infected cells will end up in locations or situations where the drugs have no effect. Some promising results have been seen, but further investigation is required.

Elimination of latently infected T cells

As virus in the latently infected cells is not usually replicating it cannot be seen by the immune system and so avoids destruction. One idea is to encourage this silent virus to become active and replicate again, so that ART and the immune system can kill the infected cells. Several ways of 'waking up' latently infected cells are being looked into, such as treating with the cytokine IL-7 or activating NF-κB with a drug called prostatin. These molecules are normally produced by cells and can increase the activity of infected cells, making the virus they produce visible to the immune system. Alternatively, drugs such as the histone deacetylase inhibitor Vorinostat or DNA methylation inhibitor decitabine are able to artificially 'switch on' the expression of genes, including the integrated HIV DNA, forcing the virus to make itself visible to the immune system. Some promising results have been seen in patients testing these therapies; however the side effects can be harmful. More research needs to be done to make these treatments safe for clinical use.

Therapeutic vaccination

In this case, vaccination is used to try and boost the ability of the immune system to fight off HIV infection. So far there has been no success with this approach, however recent results from a monkey model of HIV disease were encouraging, suggesting that it may be worth continuing to investigate this method.

HIV vaccine

One of the ultimate goals of HIV research is to develop a vaccine that prevents people from becoming infected. This would be of particular benefit to underdeveloped countries who cannot afford long term drug treatment.

So far, several vaccine candidates have been produced, and have been halted at various stages of the validation process. Generation of a suitable vaccine to HIV is more difficult than for other infectious agents for two main reasons:

- HIV is able to change itself very rapidly, so that the immune system constantly has to readjust its counterattack. This means that some virus will always escape detection and is free to continue to replicate and infect new cells.
- There are multiple different strains of HIV, which while similar, appear as different invaders to the immune response that would be generated by a vaccine. So any vaccine would have to produce an immune response that recognised viruses of all different types.

2.7. Animal models

HIV vaccines are usually tested first in monkeys, normally in a species called macaque. Macaques have their own version of HIV (called simian immunodeficiency virus (SIV)) which causes a similar disease in them to HIV in humans. The immune response observed in the macaque after vaccination is not exactly the same as in humans, which makes this model less than ideal for seeing if vaccines are effective against infection. Recently however, a mouse model has been described which shows a very similar pattern of immune response to that seen in humans. Put together, results from both these animal models will be helpful in working out which vaccine candidates should go into human clinical trials.

2.8. Clinical trials

Most initial approaches in making an HIV vaccine have targeted the envelope of the virus, in particular a viral protein called gp120. At least 13 different vaccines against this part of the virus have been tested in early stage clinical trials, with very little success.

A promising approach to vaccination is now thought to be one that stimulates a much broader immune response – producing HIV-specific antibodies as well as CD8+ T cells that are capable of killing HIV infected cells.

The largest AIDS vaccine trial so far was begun in Thailand in 2003 with a regimen called RV 144. Over 16,000 Thai volunteers were vaccinated and then asked to be tested for HIV every six months for three years, as well as receiving education on how to avoid being infected with HIV. The vaccination program was stopped in 2006 and the results released in September 2009. HIV infection rates were reduced by 31.2% in the vaccinated group compared with those who did not receive the vaccine. While these results showed there was only a limited amount protection to HIV after this 6-injection vaccine, a number of positive aspects were observed.

The RV 144 vaccination strategy made use of the two different sides of the immune system. The first injection, called the ‘primer’, was made up of components that activated the ‘cell-mediated’ immune response, which stimulates CD8+ T cells that are able to kill HIV infected cells. The following five injections, called ‘boosters’, caused the production of HIV-specific antibodies able to kill the virus. This is part of what is known as the ‘humoral’ immune response.

Both vaccine components were tested individually and failed to give any protection from HIV infection. So the results of the RV 144 clinical trial show that the combination of the different

parts of the immune system may be useful for a successful vaccine. This is an important step in the right direction in the fight against HIV and gives us hope that the answer may be just around the corner.

3. Ethical, Legal and Social Aspects (ELSA)

In this section you will find a number of opinions and incentives for discussion in class on ethical, legal and social aspects (ELSA) related to HIV.

3.1. Introduction

HIV/AIDS is a globally significant disease, with significant burdens of disease in all countries, especially in the developing world. It cannot be cured, though with the right treatment people can live with minimal symptoms (though some side effects of treatment) for many years after infection. In much of the world treatment is hard to come by and expensive, in part due to the roles of the pharmaceutical industry and the intellectual property system. In addition, because two of the main routes of transmission of HIV (sexual intercourse and injecting drug use) are topics which draw intense public debate and frequent moralism, the topic of prevention is often fraught with controversy. Finally, even where effective prevention and effective treatment is available, the psychology of risk, and social vulnerability, may lead people to become exposed to HIV unnecessarily.

3.2. Prevention

There are two broad strategies for preventing HIV transmission. The first is to take steps to protect oneself from being exposed to HIV. Since the chances of becoming exposed to HIV other than through a recognised “risk behaviour” are now known to be virtually nil, prevention efforts then focus on (a) minimising high risk behaviours and (b) making high risk behaviours safer. In settings where the main mode of viral transmission is through sexual intercourse, prevention efforts have emphasised variously the use of barrier methods of contraception (condoms, in particular), sexual abstinence, and sexual fidelity within relationships. The precise balance of emphasis given to these is controversial both in terms of advice and health promotion “on the ground” and within the circles of international aid and health policy.

The ethics of health promotion and public health are inevitably entangled to a greater or lesser extent with sexual morality, culture, attitudes to sexuality, gender (in)equality, and the degree to which people feel comfortable and empowered to discuss sexuality and sexual behaviours with their partners and others. Similarly, where the main mode of transmission is

via injecting drug use, the main prevention methods (in particular the use of safe needle disposal, free distribution of clean needles, and the discouraging of needle sharing, which can all be highly effective in reducing transmission rates, run up against the ethics and politics of drug use and "The War on Drugs". In both these debates around safe sex and around safer injecting drug use there is a tension between a pragmatic utilitarian approach which focuses on "harm reduction" and a more principled, and sometimes highly "moralistic", approach which links safety to reduction of behaviours considered wrong for some other reason (drug use or sex outside of marriage, for instance).

The other main preventive strategy is to limit the probability that the HIV infected person can transmit HIV to an uninfected person. Some of the methods mentioned above apply just as much here (safer sex practices, not sharing needles in drug use). Another method, which has received a lot of attention in the medical literature from the mid-2000s onward, is the use of antiretroviral treatment to minimise the HIV+ person's viral load, thus minimising the chance that they can pass on the virus. Although the main reason to treat the HIV+ person with drugs is for their own health, this has been an important development as it gives a further reason to expand treatment, especially in the developing world: treatment has a significant public health benefit as well as significant individual benefits. (This argument also bypasses the negative attitude sadly often found towards HIV+ people – that HIV infection should be considered "their fault" and thus "they don't deserve treatment".)

Mention of this negative attitude to people who are HIV+ draws our attention to some other methods which are occasionally discussed and indeed practiced in the name of HIV prevention. People have been dismissed from their jobs in many countries because they are thought to pose a risk to their clients, patients or workmates – although the risk of transmission may be practically nil, even in jobs involving significant contact with blood such as surgery, provided sensible protective measures are used. In some countries, HIV has been made into a notifiable disease, and people have been required to live in supervised accommodation (quarantine, in effect). And in many countries, the criminal law has been used to punish people found criminally responsible for knowingly or recklessly infecting other people. This can be considered a prevention strategy; but it may have as much to do with stigmatising and marginalising HIV+ people. Several of these methods have been strongly criticised on human rights grounds, as well as on the more pragmatic ground that these aggressive responses are ineffective and discourage people from ascertaining their HIV status. On the other hand, it can be argued that people who are HIV+ have a responsibility to

prevent themselves from infecting others, and that deliberate infection is a serious harm which should attract criminal punishment.

An important method for preventing the transmission of HIV is the use of antiretroviral treatment in pregnant women and nursing mothers, to prevent the transmission of the virus to their unborn children or children who are breast-feeding. This is known to be safe and effective, but has attracted controversy in two different ways. First, to offer treatment to a woman only during her pregnancy and the infancy of her children may be considered unfair to her and reinforcing of an image of women as only important insofar as they are (actual or expecting) mothers. Second, there is a tension between those who would insist that breast feeding is the best approach to early child nutrition, and who would insist on this treatment-based approach as a way to support that; and those who insist that breast feeding poses an avoidable risk to the child and HIV+ women should be discouraged from breast feeding.

3.3. Testing

A persistent issue in the debates about the ethics of HIV prevention and treatment concerns the ethics of HIV testing. A consistent theme throughout the HIV era, since the first identification of the virus, has been the importance of getting tested for HIV, for three main reasons: first, to know one's HIV status so that one's health can be appropriately monitored and supported and so that one can take appropriate preventative measures to protect others; second, so that the development of the epidemic can be monitored for public health reasons; and, more recently, so that one can access treatment. However, at every stage there have been countervailing factors which discourage people from seeking testing. Especially in countries which have take a more punitive public response to HIV, but everywhere where HIV+ people are subject to stigma, discrimination, fear, and, not infrequently, hate crimes, there is a serious disincentive to finding out one's HIV status. Even under ideal conditions, people may fear the disclosure of their diagnosis by health professionals or others, in breach of confidentiality. The guidance to professionals on when they may or should breach confidentiality to disclose to a partner or other interested party that the HIV+ person is HIV+ (or indeed that they have been tested) is frequently obscure and may in any case be disregarded. Particular concerns arise in the context of disclosure to insurance companies or employers; on occasion insurers have been known to refuse to insure, or insure only at higher premia, people who have disclosed that they have been tested for HIV, even if the test proved negative.

In part this stigma around testing itself, rather than HIV status as such, is explained by the linkage, in the public mind, of HIV to socially disapproved behaviours or membership of marginalised groups. A patient may not wish to disclose his or her status to his or her partner if this discloses that they caught the virus from someone else; someone else may be discriminated against if it becomes known that they've been tested (though negative) if it is assumed that this means they must be gay; and so on. Sometimes there is an association between a measure which may be sound public health policy and a socially stigmatising attitude: thus, there remains controversy in many countries whether sexually active Men Who Have Sex With Men should be allowed to donate blood, as they are considered automatically to be at higher risk of carrying blood borne viruses such as HIV, whether or not this bears any relationship to their actual viral status or sexual behaviours.

This debate relates back to an earlier debate where in several countries major public health disasters occurred because blood products contaminated with the HIV virus were put into clinical use (blood for transfusion, Factor VIII and IX for the treatment of haemophilia). While it is now generally thought that what went wrong in these cases had more to do with inadequacies in the safe management of blood banks and blood product safety than to do with the behaviour of donors as such, it is still often thought that it is sound and ethical policy to restrict who may donate as part of ensuring the biosafety of blood products.

A current issue concerns whether some groups of people should be compulsorily tested (for instance, pregnant women), especially in high prevalence countries. A slightly less intrusive approach is to "mainstream" HIV testing (as with testing for some other common diseases) in primary care, and to make HIV testing offered to all on an opt-out basis as part of routine infectious disease screening in primary care. Here there is a tricky debate between those who maintain that we have a duty to know our HIV status in order to protect people who are not infected from the risk of infection, and those who maintain that even today an HIV diagnosis is distressing and life-changing so people should actively consent to HIV testing. It might be argued that people have a right not to know their HIV status (as has been argued frequently with genetic testing for inherited disorders). But the better view is that people have a responsibility to know their status, but that this must be balanced with a clinical interest in sensitive and consensual testing, and a social justice interest in preventing discrimination and stigma.

3.4. Treatment

HIV may now be considered a treatable chronic illness, thanks to the development of the combination therapies from the mid-1990s onwards. However, treatment poses certain ethical issues, which can be broken down into clinical issues; public health issues; and global justice issues.

Clinical issues

Because HIV evolves so rapidly in each patient, and because a driver of such evolution is the virus's response to the drugs used to treat it, the use of drug therapies requires careful clinical management and regular, long-term contact with patients. Starting and stopping therapies ad hoc, non-adherence to drug therapy regimes, failing to adjust the precise mix of drugs used when treatment appears to be failing, can all influence the effectiveness of treatment and the evolution of the virus with serious consequences for the health of the patient – and, potentially, to public health (see below). There are clinical debates about at what stage in the development of HIV illness in the patient to commence drug treatment which are both about the clinical success of treatment (or otherwise) and about cost-effectiveness in the use of the drugs.

Many of these issues are particularly challenging in developing world settings, where the ability to monitor treatment may be limited by scarcity of money, clinical facilities and staff. Similarly, if treatment is only available to a limited extent, we may face the clinically important issue that a woman who is given antiretroviral therapy to prevent transmission of the virus to her unborn child or to the children she is nursing may have treatment stopped at a certain point, which will affect how she is treated (if at all) thereafter.

Public Health Issues

Treatment does not benefit solely the person treated. Treatment of HIV+ people has an important role in preventing the spread of the infection as noted above. But it also has a huge benefit in terms of protecting economic productivity, social order, reducing the number of AIDS orphans, preserving family structures, and promoting hope. There are excellent public health reasons for expanding treatment which go well beyond the purely medical. On the other hand, incautious or inappropriate use of treatment plays a part in the development of resistant strains of the virus. This is especially evident when one considers the way that HIV, through its role in depressing the immune system, makes the HIV+ person significantly more

vulnerable to other infectious diseases, notably tuberculosis, which is in its turn developing increasingly dangerous treatment-resistant strains.

Global Justice Issues

A heated issue continues to be access to treatment. Three major barriers to treatment can be noted. First, treatment requires testing, and in societies where there is strong stigma against HIV positive people, people may be unwilling to come forward for testing. This relates to a wider issue concerning the "culture" of HIV: HIV infection, testing and treatment form part of a complex web of social practices and attitudes to illness, sexuality, family life, religion, healthcare… in every society. Appropriate intervention to prevent and treat HIV will always require some level of engagement with this culture, and there are subtle and problematic issues involved in such engagement especially cross-culturally. Much important research in HIV treatment is actually social science research, including research into the interrelationships between human rights, health, and ethics.

A second major barrier to treatment is the lack of sufficient healthcare infrastructure in many parts of the world most affected by HIV. "Rolling out" treatment in resource-poor or widely scattered communities poses serious difficulties. This has led some public health specialists to argue that HIV is a disease of poverty. Treating people with limited resources leads to difficult choices of fair distribution and priority setting, which are entwined with very pragmatic questions of public health strategy. For example, should we concentrate on treating those people who are easiest to get to? Is this an ethical criterion? Or merely one of convenience?

A third major barrier to treatment is suggested by the second: scarcity in the short term is almost always explicable by structural factors and incentives which could be changed, but which seem like "facts of life" at close up. For instance – primary care in rural settings may be thinly spread, and in part that is down to sheer geography. But it is also down to decisions upstream about how many healthcare workers to train; how attractive it may be to healthcare workers to leave to work overseas once trained (the "brain drain"); economic decision-making about healthcare financing; and so on. Much of the debate has focussed on one particular structure: the use of the intellectual property rights system to entrench (albeit temporarily) the right to price antiretroviral drugs at high profit margins and to prevent the manufacture of cheap "generic" copies while the patent lasts. Drugs which may be affordable in the developed world may be quite unaffordable save to a very few in the developing world.

3.5. Research ethics

This issue of affordable access to treatment spills over into debates about the ethics of clinical trials, as much as about the ethics of treatment pricing itself. Trials designed to test cheaper, more sustainable treatment approaches have been tried in various countries, but there are difficult ethical controversies about whether people who are in such trials should be entitled to continue treatment once their time “on study” is over, about whether using dummy (“placebo”) control groups is acceptable when in the developed world the control group would receive standard active drug treatment, and (in vaccine or microbicide trials) whether people who become infected while “on study” should be given treatment.

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