To what extent can early antiretroviral therapy play a role in the prevention of Human Immunodeficiency Virus infection?

University of Groningen
Bachelor thesis of Biomedical Science

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May 2012

Under the guidance of
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Medical Microbiology; Molecular Virology

Abstract

Treatment with combinations of different antiretroviral drugs, known as combined antiretroviral therapy, has declined morbidity and mortality due to AIDS. Antiretroviral drugs are also used as post-exposure prophylaxis and pre-exposure prophylaxis. *Science* declared the results of a study with compelling new evidence showing that antiretroviral drugs (ARVs) can prevent heterosexual HIV transmission as breakthrough of the year for 2011. Along with positive results of studies on antiretroviral therapy as pre-exposure prophylaxis of HIV infection, this study started enthusiasm for antiretroviral therapy as a tool for HIV prevention. High costs, non-adherence, drug resistance, drug toxicity and risk compensation are factors compromising the role of antiretroviral therapy in prevention. Although several studies have shown positive results, antiretroviral therapy is not the final solution in prevention of HIV infections. Priority of ART should remain for those with untreated advanced disease. However, when applied properly and in combination with the existing tools of prevention antiretroviral therapy can have a significant role in prevention of HIV infection worldwide.

Contents

1. Introduction

1.1 Human immunodeficiency virus

Human immunodeficiency virus (HIV) is a virus belonging to the family of *Retroviridae* that causes acquired immunodeficiency syndrome (AIDS) (Douek et al. 2009). HIV interferes with cells of the immune system that express CD4 protein on their surface. Especially CD4+ lymphocytes, also known as helper T cells, play an important role in HIV infection. The virus enters the cells to replicate itself. Due to this process CD4+ T cells are killed, either directly by the virus or by apoptosis induced by CD8+ T cells (Pantaleo et al. 1994). Eventually, the number of CD4+ cells declines which will lead to a functional reduction of the immune response. This dysfunction of the immune system is the AIDS stadium and can lead to different kinds of opportunistic, potentially lethal infections.

1.2 Prevalence

Since the virus was recognized in 1981 more than 65 million people have been infected with HIV worldwide and over 25 million people have died of AIDS (Merson, 2006).
According to the World Health Organization (WHO) there were 33,4 million people infected with HIV worldwide in 2008. Although the number of people living with HIV is still increasing every year, prevalence seems to have leveled off (fig. 1). This could be attributed to better sexual education and improved therapy options. Moreover, the academic journal *Science* declared the results of a study with compelling new evidence showing that antiretroviral drugs (ARVs) can prevent heterosexual HIV transmission as
breakthrough of the year for 2011.

1.3 Aim

The aim of this paper is to give an overview of the role of early antiretroviral therapy (ART) in the prevention of HIV infection worldwide.

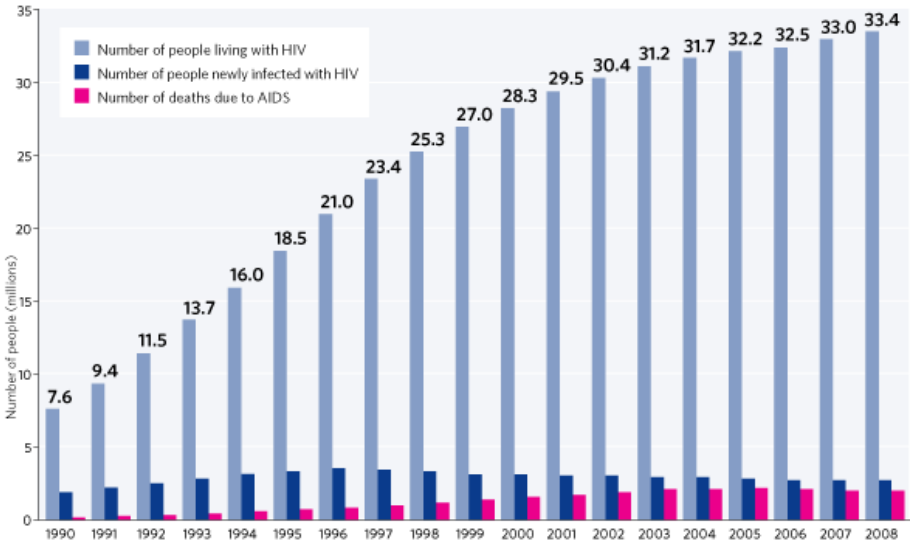

Figure 1 Worldwide number of HIV infected people from 1990 to 2008
http://www.who.int/hiv/data/global_data/en/index.html

2. Human immunodeficiency virus

2.1 Classification into groups and subtypes

HIV can be divided genetically into two major types, HIV-1 and HIV-2. Although HIV-2 is known to cause AIDS, it is less transmittable and less virulent than HIV-1 (Kannangai et al. 2012). HIV-2 is an epidemic in predominantly West-Africa and infections with the virus are very limited outside that area (Santiago et al. 2005). Most research has been done about HIV-1, which can be divided into a major group, called M, and several other groups with group M being responsible for more than 90% of all HIV infections worldwide. It is believed that these groups were transmitted independently from each other from animals to humans, but the subtypes within a group were not. Subtypes for group M range from A to K and recombinant forms originated from recombination between subtypes (Sharp et al. 2011)

2.2 Structure of HIV

HIV is roughly spherical and 120 nm in diameter. It contains two single strands of RNA, which are bound to several proteins like HIV-1 reverse transcriptase and integrase. The RNA is enclosed by a capsid, which in turn is enclosed by a envelope membrane originated by budding off from the host cell. The plasma membrane contains the glycoprotein gp120, which can bind to the CD4 protein expressed on host cells. Transmembrane glycoprotein gp41 anchors gp120 to the host cell by a non-covalent binding (Kwong et al. 1998).

2.3 Infection with HIV

Entry of HIV in the host cells starts with binding of the gp120 viral protein to the CD4 protein, acting as a primary receptor, on the host cell surface (Wyatt et al. 1998). Due to this binding gp120 undergoes conformational changes exposing a binding site for specific secondary chemokine receptors. Mainly CCR5 on macrophages and CXCR4 on T cells serve as these coreceptors (Kwong et al. 1998). The interaction between gp120 with CD4 and a coreceptor causes exposure of the fusion domain of gp41 that initiates fusion and entry into the host cell (Curelli et al. 2012). After fusion of the two cell membranes the enzymes reverse transcriptase, ribonuclease, integrase and protease are being transported to the nucleus of the host cell via microtubules. During this transport, reverse transcriptase transcribes the viral RNA to cDNA (fig. 2). This cDNA in combination with integrase, reverse transcriptase and other viral proteins is transported into the nucleus where is inserted in the genome of the host cell by integrase (Zheng et al, 2005). Once the viral DNA is inserted it is called a provirus and is in a latent state. The provirus will stay latent until an antigen is presented to the CD4+ cell, causing the cell to start transcription of its genome. To be replicated several host cell transcription factors are needed. NF-kB is a transcription factor that plays a major role in viral replication because the viral DNA has two binding sites for NF-kB, this way mediating its own transcription (Hiscott et al. 2001). During replication the provirus is transcribed to mRNA, which is then spliced in the nucleus and transported to the

cytosol to be translated into viral proteins. Two of these synthesized proteins are Tat and Rev. Tat interacts with NF-kB and will enhance viral replication, acting as a positive feedback (Hiscott et al. 2001) The Rev protein, when accumulated, will bind to newly produced mRNA in the nucleus and prevent it from being spliced (Pollard et al. 1998). After being transported to the cytosol translation of the unspliced mRNA will produce the proteins Env, reverse transcriptase and integrase and Gag. The last three will assemble with two strands of the unspliced mRNA and be encapsulated by a layer of membrane that contains Env as viral envelope protein. A final process, known as maturation, occurs during budding of the virus particles. The viral protein protease will cleave the proteins in the core into a final form, preparing them for infecting new host cells (Pollard et al. 1998). Using different ARVs to arrest the lifecycle of HIV, researchers found that inhibiting entry of the virus to the host cell and inhibiting transcriptase activity stopped killing of CD4+ cells. Blocking later stages in the lifecycle did not stop the declining number of CD4+ cells. An explanation can be found in the process of reverse transcriptase, which does not work well in most CD4+ cells and incomplete DNA intermediates will accumulate in the cytoplasm. This accumulation is sensed by the cell and will trigger apoptosis (Doitsh et al. 2010)

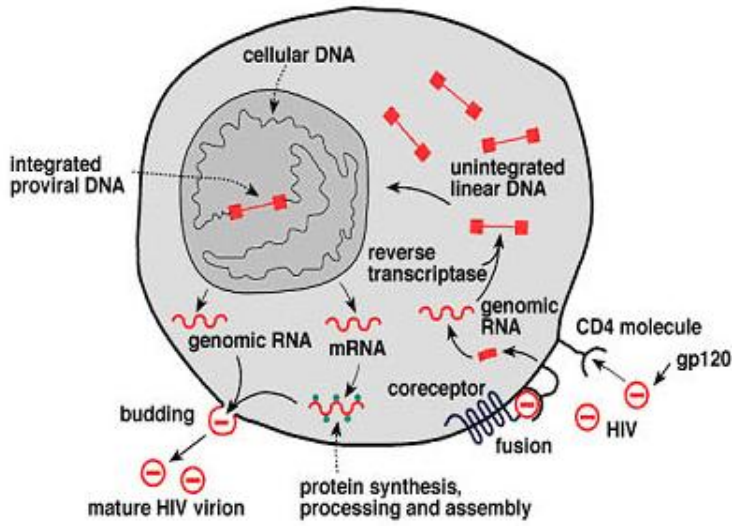

Figure 2 HIV replication cycle
Adapted from National Institute of Allergy and Infectious diseases, USA
http://www.web-books.com/eLibrary/Medicine/Infectious/AIDS_HIV.htm

3. Transmission of HIV

Three main routes of HIV transmission have been identified: sexually, blood to blood contact and vertical transmission.

3.1 Sexual transmission

Most HIV infections, an estimated 75 to 85 percent, are caused by unprotected sexual acts (Royce et al. 1997). Virus infection can occur when secretions of an infected person come in contact with genital, oral or rectal mucous membranes of another. Research shows that the risk of contracting HIV during unprotected intercourse differs between developed and developing countries. In developed countries the risk of contracting HIV when having intercourse with an infected person is 0.04 percent for female to male transmission and 0,08 percent for male to female transmission. In developing countries this risk is 0,38 and 0,30 respectively (Boily at al. 2009). Lower sexual education, lower access to condoms and ART in developing countries all contribute to this difference. Furthermore, HIV transmission during unprotected anal intercourse with an HIV-infected person is 1,7 percent per act, explaining why homosexual men are especially susceptible to infection.
While HIV transmission via sexual intercourse can only be avoided by abstinence, it can be substantially lowered by use of condoms. According to a 2007 report of the WHO correct use of a condom during sexual intercourse reduces the risk HIV transmission with 85 percent.

3.2 Blood to blood transmission

Blood to blood contact is another transmission route of HIV. Not only blood transfusion but open wound contact and reuse of needles are sources of transmission. The risk of transmission when HIV infected blood is transfused to a not infected person is highest of all transmission routes. Estimates of infectivity for contaminated blood transfusion are between 88 to 100 percent (Baggaley et al. 2006). However, since in most developed countries blood donors are screened and donor blood is always checked for HIV, chances of transmission via blood transfusion are small. The same goes for transmission via needles. In the developed medical world needles are not reused. Unfortunately this is not be the case in developing countries and with intravenous drug users. Infectivity for intravenous drug users is estimated between 0,67 and 0,84 percent. Estimates of infectivity with confirmed contaminated needles are as high as 6,9 percent. (Baggaley et al. 2006)

3.3 Vertical transmission

A third transmission route of HIV is vertical transmission. Transmission can occur in the uterus, at birth or after birth via breast feeding. Without medical intervention the change of HIV transmission from mother to child is 25 percent (Coovadia, 2004). Chance of transmission can be lowered with ART treatment, a caesarean section instead of natural birth and avoidance of breast feeding.

4. Antiretroviral therapy

Currently, an infection with HIV cannot be cured. However, extensive research to HIV has been done and since 1995 treatment strategies for lowering viral load began to improve significantly. Before that time treatment with one antiretroviral drug (ARV) proved to be not effective in treatment of HIV infection because of the high rate of unspecific mutations and the resistance of HIV as a consequence. Treatment with combinations of different ARVs, known as combined antiretroviral therapy (cART) has dramatically declined morbidity and mortality due to AIDS (Palella et al. 1998). Numerous ARVs have been developed which can be divided into different classes since ARVs can interfere with different steps in the life-cycle of HIV (table 1).

4.1 Combined antiretroviral therapy

Most cART regimens are composed of three ARVs from two different classes. The U.S. Department of Health and Human Services provides guidelines for cART. As of June 2011 preferred regimens are two nucleoside reverse transcriptase inhibitors combined with one protease inhibitor, combined with one integrase inhibitor or combined with one protease inhibitor (Department of Health and Human Services, 2011). Although spectacular progress has been the finish line is not made yet. In a meta-analysis of 21 treatment groups only 46 percent of the participating patients were able to reach the targeted viral load (Bartlett et al, 2000). These results may underestimate the effects cART had on disease progression because the targeted viral load was set extremely low. It cannot be said that people who did not reach targeted viral load did not benefit from cART. Like mentioned previously, cART has dramatically declined morbidity and mortality due to AIDS. However, there are still several problems cART faces like short-term intolerance, long-term toxicity, drug resistance, risk compensation and high costs which will be discussed in the next chapter (Saag, 2001).

Table 1. Different classes of ARVs

Class	**Mechanism**	**Example**
Early inhibitors	Inhibit fusion of HIV with host cells	Maraviroc (CCR5 inhibitor)
Nucleotide/Nucleoside reverse transcriptase inhibitors	Analogues of deoxynucleotides compete for incorporation in viral DNA chain. Once incorporated, viral DNA synthesis is stopped	Abacavir Tenofovir Zidovudine
Non- Nucleoside reverse transcriptase inhibitors	Bind to reverse transcriptase inhibiting its activity	Efavirenz Etravirine
Integrase inhibitors	Inhibit integrase	Raltegravir
Protease inhibitors	Inhibit protease	Saquinavir

4.2 Post exposure prophylaxis

For people that have been exposed to HIV, think for example of needle-stick injuries in health care, the Department of Health and Human Services in the U.S. recommends post exposure prophylaxis (PEP) (Smith et al. 2005). A case-control study of health-care workers with percutaneous exposure to HIV showed an 81 percent decrease in HIV transmission if zidovudine was administered after exposure (Cardo et al. 1997). Several other observational studies show comparable results but there are several drawbacks to these studies. Participants were not randomly assigned and the sample sizes are very small to produce firm conclusions. However, results of the discussed observational studies suggest that 72 hours after risk of infection PEP is much less effective. Furthermore, duration of PEP should be at least 28 days (Smith et al. 2005).

4.3 Pre-exposure prophylaxis

Unlike PEP, which is taken after high-risk exposure, pre-exposure prophylaxis (PrEP) is a prevention therapy started before high-risk exposure and has to be continued throughout periods of high-risk. In a randomized study, 2499 HIV-negative homosexual men and transgender women were administered either oral emtricitabine/tenofivran or a placebo. An incidence reduction of 44 percent was found in the group who took PrEP compared to people who took a placebo (Grant et al. 2010). Comparable results were found in a study of PrEP in heterosexual HIV discordant couples (Mujugira et al. 2011). Although PrEP may be promising as a new prevention tool for HIV, further research needs to be done because two other studies did not show a significant reduction of infection risk due to PrEP (Celum et al. 2012).

5. Role of antiretroviral therapy in prevention

5.1 Breakthrough of the year 2011

The search of new prevention tools for HIV infection is a hot topic. *Science* declared the results of the paper *Prevention of HIV-1 Infection with Early Antiretroviral Therapy* as scientific breakthrough for the year 2011. The study involved over 1763 mostly heterosexual and all HIV discordant couples with the HIV infected partner not in need of ART at the beginning of the study. The couples were randomly separated into two equally large groups. One group received oral ART immediately (immediate ART group) and the other group received oral ART when AIDS-related illnesses developed (delayed ART group). In the delayed ART group, 27 HIV transmission occurred while in the immediate ART group only 1 transmission occurred. Lowered viral load reduced HIV transmission (Cohen et al. 2011). Along with successful trials for PrEP and three studies on ART as prevention, the study described above started enthusiasm for ART as a tool for HIV prevention. Furthermore, lowering viral load, being a major risk factor in vertical transmission, may reduce the rate of transmission from mother to child (Ryder et al. 1988). However, the rose-colored future these studies suggest may not be as near as we think, because there are several hurdles in the implementation of ART in HIV prevention.

5.2 Identifying infection

There are around 34 million people infected with HIV worldwide and only an estimated 6,6 million are getting ART (UNAIDS, 2011). This could be partially contributed to high cost and logistical difficulties ART faces, but mainly to unawareness of being infected with HIV. In Lesotho a national campaign was started in 2004 to promote HIV testing. In five years only half the adult population had been tested (Ministry of Health and Social Welfare Lesotho, 2010). A substantial proportion of the population is unaware of infection and remains untreated. For ART to be effective in prevention more people should get tested and all

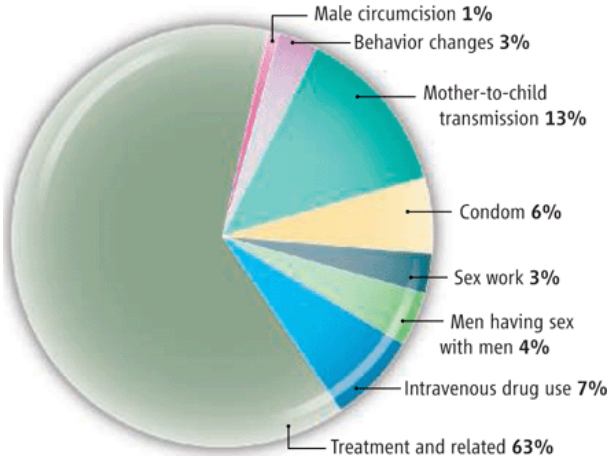

Figure 3 Global HIV program funding 2011
Derived from Schwartländer et al. 2011

positive tested people should get ART for a lifetime which could be difficult to adhere to. Furthermore, more people getting ART will be a severe burden on global funding for HIV. For 2011 63 percent of the current basic program funding supported ART and care related services with only twenty percent of the HIV infected getting ART (Fig. 3).

5.3 Adherence to ART

Inadequate adherence is a problem ART faces since its beginning and is attributed to different factors including high pill burden, economic instability and adverse drug effects (Ammassari et al. 2002). A lot of research has been done on how to improve adherence to ART. High pill burden has decreased substantially with help of fixed-dose combinations (different ARVs in one pill) but other factors lowering adherence are more complicated to target. To be effective in prevention not only people with AIDS-related illnesses but also those who are symptom-free need to get ART for a lifetime. In this case a major factor that compromises adherence might be adverse drug effects and lack of symptoms after nonadherence.

5.4 Drug resistance

A consequence of inadequate adherence to ART is that it acts as a selection filter for mutations in HIV which will lead to drug resistance (Sethi et al. 2003). According to Friedland and Williams the relationship between inadequate adherence and drug resistance is bell shaped. Complete adherence and complete nonadherence to ART are associated with lowest probabilities of resistance. Intermediate levels of adherence increase the risk of mutations in HIV, this way developing drug resistance (Friedland et al. 1999) Drug resistant HIV strains have already been found in untreated patients and providing ARVs on a bigger scale would probably increase drug resistance. In Uganda, where ARVs were first available, drug resistance in ARV naïve individuals is significantly higher compared to other African countries (Hamers et al. 2011) Moreover, symptom-free people that get ARVs for prevention and not directly for their own health are more likely to adhere inadequately to ART (Shelton, 2011).

5.5 Drug Toxicity

For people who take ARVs for their own health the benefits of ART far outweigh the possible consequences and adverse effects. Toxicity of ARVs becomes a concern when symptom free HIV infected people take ARVs for prevention. Short-term adverse effects like dizziness and nausea have been reported but ARVs may also cause long-term toxicity which are still being defined (Max et al. 2000). Research shows that nucleoside reverse transcriptase inhibitors not only target viral reverse transcriptase but also mitochondrial polymerase. This mitochondrial toxicity explains part of the long-term toxicity of the drugs (Brinkman et al. 1998.) Furthermore, Tenofovir (table 1), which was included in all ART prevention trials today, is associated with nephrotoxicity (Fernandez-Fernandez et al. 2011).

5.6 Risk compensation

Another factor that not only affects ARVs but all prevention strategies for HIV is risk compensation. A decrease in perceived risk causes an increase in risky behaviour. Studies among homosexuals, heterosexuals and intravenous drug users show that the availability of PEP has been associated with significant increases in risky sexual behaviour (Casell et al. 2006). In an community intervention in Uganda promotion of condoms did not reduce HIV risk because it was offset by increases in the number of sex partners (Kajubi et al. 2005). It is of vital importance to manage the optimism caused by prevention strategies. This could be done by clearly explaining the limitations a strategy has. Simply handing out condoms or offering PEP to people at risk will not be effective in prevention if no behavioral change is promoted.

5.7 PrEP and prevention

PrEP is taken before high-risk exposure and thus a pure tool of prevention. However, most of the drawbacks summed up above also apply to PrEP. Moreover, two studies found that PrEP significantly reduced transmission but two other studies failed two show significant results (Celum et al. 2012). Furthermore, it would be very hard to determine who is eligible for PrEP and who is not. Would only HIV negative partners in discordant couples be at such a substantial risk or should all people with multiple sex partners be eligible for PrEP? Another worry of using PrEP on a substantial scale is that some individuals would take PrEP sporadically and then engage in risky sex, which would have detrimental effects (Shelton, 2011).

6. Conclusion

Extensive research has been done about HIV and possible ways to prevent transmission of the virus have been developed. Since cART became available morbidity and mortality due to AIDS have dramatically declined. ART definitely can play an important role in prevention of HIV infection but there is a need to be cautious in its implementation and several drawbacks should be taken into account. For ART to be effective in prevention it should be cheaper and more user-friendly, this way providing ART where the need is high and avoiding drug toxicity and non-adherence.

Although several studies have shown positive results and *Science* declared one of them as breakthrough of the year for 2011, more research needs to be done focusing on the other effects of ART when applied on a much bigger scale, as is the case when used in prevention. Furthermore, it is especially important to develop strategies to prevent ART from interfering with current prevention methods as condom use and behavioral change.

To conclude, ART is not the final solution in prevention of HIV infections and priority of ART remain for those with untreated advanced disease. However, when applied properly and in combination with the existing tools of prevention ART can have a significant role in prevention of HIV infection worldwide.

Acknowledgements

I thank Prof. Dr. J.C. Wilschut for providing information and for his evaluations.

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