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The Sub-Saharan African HIV Epidemic - "Successes and Challenges"

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1. Introduction

The global impact of the human immunodeficiency virus (HIV) pandemic is enormous. To date, more than 25 million lives have been claimed by the acquired immunodeficiency syndrome (AIDS) and over 33 million people are currently estimated to be HIV-infected. Ninety-five percent of these people infected with HIV live in developing countries. Sub-Saharan Africa is the region that is hit hardest by the HIV pandemic.

During the quarter century since the first reports of a novel immunodeficiency syndrome in 1981, great advances have been made in HIV diagnosis, prevention and care. The first protease inhibitor (PI) was approved in 1996, marking the start of the highly active antiretroviral therapy (HAART) era. From then on, HIV-infections were no longer inevitably associated with AIDS and death, but could be viewed as a chronic condition [Merson, 2006; Sepkowitz, 2006]. Currently, the antiretroviral armamentarium includes over 20 different drugs and more are in the pipeline. The use of HAART can result in effective, long-term suppression of the virus with consequent recovery of the patient's immune system. Unfortunately, complete HIV eradication is still not feasible. Moreover, it is apparent that the virus generally resurges to pre-treatment levels within months after ART withdrawal. Patients therefore need a life-long commitment to their treatment.

The logistic and monetary costs associated with such long-term HIV-care are high. HIV monitoring and treatment was therefore initially only available in resource-rich countries. Great efforts and large funds were needed to make ART more widely available. This awareness and initiatives, such as the "United States' President's Emergency Plan for AIDS Relief" and the "Global fund for AIDS, TB and Malaria", resulted in an unprecedented roll-out of treatment since the turn of the millennium [United Nations]. The increase in HIV-infected individuals receiving ART has been especially large In Sub-Saharan Africa where over the last decade, many ART programs took off, treating millions of HIV-infected patients. Despite these impressive accomplishments however, monitoring and research facilities in low-income countries (LICs) still lag behind.

There are great differences between HIV care in resource-rich and LICs. First, due to limited resources, the number of clinics, health care providers and other necessities for quality health care are lower in LICs compared to high-income countries. Second, HIV is generally transmitted via heterosexual contact in African countries, whereas homosexual contacts and intravenous drug use are the main routes of transmission in western countries. Moreover,

due to differences in genetic make up there may be different reactions to the virus and its treatment between different populations. Third, the virus itself differs between various geographical areas. While subtype B is the main HIV subtype in Europe and the United States, it is rarely seen in Sub-Saharan Africa, where subtype C is the prevailing HIV subtype.
The on-treatment HIV-RNA-level is associated with a patients' clinical outcome. Therefore, western guidelines recommend regular HIV-RNA monitoring in all patients receiving ART. Roll-out strategies in LICs on the other hand were initially mainly focused on providing as many patients with antiretroviral drugs (ARVs) as possible, thereby limiting the resources left for laboratory monitoring. As regular HIV-RNA testing is not feasible in many, Sub-Saharan African ART programs, treatment decisions are frequently solely based on clinical or immunological parameters. However, the correlation between these parameters and virological outcomes appears to be marginal [Kantor et al., 2009; Keiser et al., 2009; Reynolds et al., 2009b]. Moreover, making predictions on long-term treatment outcomes is difficult, as the virological effects of these programs are not clear and other surrogate markers for clinical outcomes are not available.
Despite the above mentioned difficulties, great progress has been made regarding HIV care in Sub-Sahara Africa. However, challenges remain. Both successes and challenges regarding prevention and treatment of HIV as well as viral resistance development and treatment of co-morbidities will be addressed in the following chapter.

2. Prevention

In 2007, the WHO announced that the HIV-epidemic seemed to be levelling off. Still, over 33 million people are estimated to be HIV-infected globally, with 2.6 million people becoming newly infected annually. The overall adult HIV prevalence in Sub-Saharan Africa is estimated to be over five percent, with prevalence rates up to twenty-five percent in some countries [UNAIDS, 2009]. This however means that the vast majority (more than ninety percent) is still HIV-negative. Keeping these people free from HIV, as well as preventing new generations from becoming infected, is a major challenge and should remain a priority on the HIV-care agenda.

2.1 Prevention of mother to child transmission

One of the great advances in HIV preventive-care has been the "prevention of mother to child transmission" (PMTCT) strategies. Testing pregnant women for the presence of HIV and subsequently providing those that are infected, as well as their new-born babies, with ARVs has the potential of reducing vertical HIV transmission rates to below one percent [Paintsil and Andiman, 2007; Paintsil and Andiman, 2009]. Short-course ARVs or single-dose nevirapine (SDNVP) are frequently used for PMTCT instead of complete ART regimens in low-income countries (LICs). Such regimens have shown to be efficacious in averting many infant-HIV infections. Still, with transmission rates ranging from one to above ten percent, results are lagging behind those observed in resource-rich settings [Boeke and Jackson, 2008; Chigwedere et al., 2008; Leroy et al., 2008; Palombi et al., 2007; Tonwe-Gold et al., 2007]. Moreover, administration of SDNVP can lead to the selection of non-nucleoside reverse transcriptase- (NNRTI-) associated resistance mutations. There is evidence that fewer mutations are selected when other ARVs are added to the SDNVP [Arrive et al., 2007; Chi et al., 2007a]. However, the optimal combination of drugs and best time for treatment initiation in order to create a feasible and effective PMTCT strategy for

LICs, still need to be defined [Chi et al., 2007b; Lockman et al., 2007]. In addition to improving the efficacy of PMTCT programmes, the PMTCT coverage needs to be expanded. Many resource-limited countries still have a limited PMTCT-coverage; in South Africa for example only sixty percent of HIV-infected pregnant women have access to this simple, cost-effective strategy and figures are worse for several other LICs [Abdool Karim et al., 2009; Paintsil and Andiman, 2009]. These data show that, even though much progress is made in the field of PMTCT, improvements are urgently needed to prevent even more infant-HIV infections and deaths.

2.2 Vaccines

Historically, vaccine development is one of the fields in health care where major progress is achieved. Many infectious diseases were effectively prevented and some nearly eradicated. Unfortunately, results of HIV vaccine research are unrelentingly negative. Many candidate vaccines were developed, but the results proved unsatisfactory and major vaccination studies were stopped [Johnston and Fauci, 2008]. Despite these failures, some vaccines are still being tested. Most of these are directed at stimulating the immune system [Fauci et al., 2008]. Still, finding an effective vaccine in the near future does not seem likely.

2.3 Circumcision

Several other preventive strategies were analyzed and implemented, resulting in variable success rates. Male circumcision was put forward to prevent heterosexual HIV transmission since a lower female HIV prevalence was observed in Sub-Saharan African countries with high levels of male circumcision [Auvert et al., 2005; Williams et al., 2006]. However, epidemiological evidence of a direct protective effect of male circumcision on women becoming infected with HIV is limited according to some [Weiss et al., 2009]. To date, most consider male circumcision to have a significant, albeit partial, efficacy in reducing heterosexual HIV transmission [Doyle et al.; Smith et al.]. To what extend expanding circumcision coverage will contribute to combating the global HIV epidemic, still needs to be determined.

2.4 Post- and pre-exposure prophylaxis

Post-exposure prophylaxis (PEP) is a successful prevention method after incidental needle or sex accidents. In Sub-Saharan Africa however, where heterosexual contact drives the HIV epidemic, PEP provision is limited and will not substantially influence the HIV statistics. Pre-exposure prophylaxis (PrEP) on the other hand may prove to be a promising strategy. An effective agent that can be used safely by women prior to sexual intercourse and without the need for agreement from a partner would be a major contributor to preventive HIV care [Al-Jabri and Alenzi, 2009]. However, until now trials of microbicide candidates have shown disappointing results; some even suggested a boosted risk of infection as more vaginal lesions were observed in treated patients [Al-Jabri and Alenzi, 2009; Wilson et al., 2008]. Possibly gels that incorporate ARVs will be more effective as PrEP. Studies are being set up and hopefully results will come available in the coming years [Grant et al., 2008].

2.5 Antiretroviral treatment as a preventive measure

In spite of these preventive strategies it is not likely that the high HIV incidence will change in the near future. Some strategies are only partly effective and many remain grossly

underused [USAID, UNAIDS, WHO, CDC and the POLICY project; Kerr et al.]. More importantly, the development of a preventive vaccine seems to be nearly impossible and HIV-eradication can not be realised with current treatment strategies. Still, provision of ART surpasses the obvious benefits it has on an individual level. Treating HIV can be used as an essential part of prevention efforts. For heterosexual contact and for mother-to-child-transmission a clear dose-response effect was found between HIV-RNA levels and risk of HIV transmission [Fang et al., 1995; Quinn et al., 2000; Tovanabutra et al., 2002]. As these are the main routes of HIV transmission in Sub-Saharan Africa, it seems likely that bringing down individual HIV-RNA levels can make a substantial contribution to reducing the number of new infections. Indeed, such positive effects were described previously, suggesting cost-saving effects of ART due to the reduction of HIV transmission, in addition to the clear benefits of such treatment on an individual basis [Granich et al., 2009; Mayer and Venkatesh; Montaner et al., 2006]. Up till now, the roll-out of ART has not clearly reduced HIV-incidence. If a preventive effect of ART becomes more apparent as treatment-coverage increases, and as patients receive care for longer periods of time, will largely depend on the number of patients experiencing virological failure.

2.6 Awareness

Creating awareness about the risks of unprotected sex and other potential transmission routes, as well as providing information on advances that have been made in HIV care, is of utmost importance in reducing the stigma's associated with HIV and in motivating people to do an HIV-test. An elevated level of awareness may lead to patients seeking care at a less advanced stage of disease. As a result, chances of a good clinical response to ART will be greater. Moreover, the period that patients will have high viral loads and therefore are highly infectious, will be shorter if patients have their HIV tested and treated at an earlier stage. Continued monitoring of HIV incidence, and possibly mathematical modelling studies, are needed to further calculate the preventive and cost-saving effects of ART expansion programmes.

3. Treatment

HIV leads to AIDS and death when left untreated. ART provides clear benefits for those infected and rendered HIV-infection a manageable chronic condition. Access to treatment increased considerably over the last decade. Still, by the end of 2008, less than half of the people in need of treatment in Sub-Saharan Africa actually received ART [UNAIDS 2009] and the United Nations endorsed target of "universal access by 2010" has not been met [WHO, 2006b]. It was recognized that access to treatment is especially limited for certain groups of people, such as those living in rural settings [Crowley et al., 2009]. Therefore, continued efforts are needed to increase the availability of ART even further.

3.1 When to start ART

When to start ART in HIV-infected individuals remains a controversial issue. Initially, treatment was deferred until CD4 counts dropped to below 200 cells/mm^3 in most LICs [Wood et al., 2005]. In western settings it is common practice to initiate ART earlier, when CD4 counts are less than 350 or even 500 cells/mm^3, as various studies suggest improved treatment outcomes at higher CD4 thresholds [Braithwaite et al., 2008; Emery et al., 2008; Kitahata; Sterne]. Benefits of an earlier treatment start may be even greater in LICs

compared to high-income countries, due to higher rates of opportunistic diseases and mortality there. However, the number of people eligible for ART will increase as CD4 treatment-initiation thresholds move up, putting extra pressure on the already fragile health care facilities and limited resources. A mathematical modelling study on the other hand reported that an increase of the CD4 treatment-initiation threshold (to 350 cells/mm^3) would reduce morbidity and mortality while remaining cost-effective, in the South African context [Walensky et al., 2009]. Moreover, the WHO recently adjusted its guidelines, recommending to start treatment at CD4 counts of 350 cells/mm^3 or less for all HIV-infected individuals [Crowley et al., 2009]. However, definite results from ongoing, international trials assessing when to initiate ART in resource-limited settings will not be available for several years.

3.2 Treatment outcomes

Overall, on-treatment, short-term outcomes of Sub-Saharan African ART programs that have access to HIV-RNA monitoring, are promising and similar to those initially observed in western settings. However, high early attrition (composed of all-cause mortality and patients being lost to follow up) is frequently observed, negatively influencing intention-to-treat results. Within a few years after treatment start, virological failure is observed in only fifteen percent of patients. It should be borne in mind though, that applied failure criteria are generally more lenient than those used in western settings [Barth RE, 2010b]. Long-term outcome data are still limited, but seem promising as well.

First-line ART regimens in Sub-Saharan Africa are generally NNRTI-based. Boosted PIs may also be used in treatment-naïve patients. Compared to an NNRTI-based first-line regimen this resulted in a slightly reduced treatment efficacy, but fewer resistance mutations [Riddler et al., 2008; von Wyl et al., 2007]. A review on clinical trials also showed that fewer nucleoside reverse transcriptase inhibitor- (NRTI)-associated resistance mutations were present in case of boosted PI-based regimen failure compared to NNRTI-based regimens [Gupta et al., 2008]. The answer to the question whether or not it is advisable to move to a PI-based first-line ART regimen in LICs will largely depend on the balance between costs, adverse events and resistance development profiles.

3.3 Adverse effects

Providing all those in need with ART is a daunting task. However, caring for those already receiving treatment poses many challenges as well. As HIV-infected people live longer, the long-term effects of the virus and its treatment become more evident. Simple, affordable treatment regimens facilitated the initial, extensive ART roll-out. However, the negative effects associated with these commonly used treatment options called for a reconsideration of widely applied treatment strategies. Mitochondrial toxicity causes neuropathy, lipodystrophy and lactic acidosis in many individuals receiving stavudine-containing ART. Therefore, it was recommended to move away from stavudine-based regimens to zidovudine or tenofovir (TDF) [Crowley et al., 2009; WHO, 2006a]. As yet, not all African countries have adopted TDF as a first-line regimen in their guidelines for financial reasons, but this may change during coming years. As TDF becomes more widely available, knowledge of its side-effects grows more important. TDF has potential nephrotoxic effects. Generally no negative effects on renal function are observed when TDF is used in a first-line ART regimen [Gallant and Moore, 2009], but little is known regarding the prevalence and nature of renal impairment in African cohorts. In one South African cohort the number of

people with severe renal dysfunction was limited [Franey et al., 2009], but future studies will have to show what the long-term effects of TDF use in African patients are. Another concern with TDF use relates to the possible increased risk of bone disease. HIV-infected individuals have an increased risk of osteopenia compared to HIV-uninfected people. This risk is increased further by the use of TDF [Jacobson et al., 2008]. It is not yet clear whether patients receiving TDF also have an increased bone-fracture risk. The increased risk of cardiovascular disease and diabetes, associated with some antiretroviral drugs, will be discussed in more detail later. These and other negative effects of long-term ARV use in various populations have to be addressed in future studies.

3.4 Second line treatment

PIs are becoming more widely available in LICs since the advent of heat-stable drug formulations. They are typically used in second-line regimens, in case of treatment failure. As currently the vast majority of patients receiving ART in Sub-Saharan Africa are receiving a NNRTI-based, first-line regimen, limited data are available on the efficacy of PI-based regimens in African settings. Good, early, virological responses were reported, but a frequent occurrence of adverse events was also observed [Castelnuovo et al., 2009a; Hosseinipour et al.]. In a large trial performed in western countries (TITAN trial) over three quarters of treatment-experienced patients achieved an HIV-RNA less than 400 copies/mL after switching to either lopinavir/ritonavir or darunavir/ritonavir in combination with an optimized backbone regimen. Results were even better if patients with any prior PI-exposure were excluded from analysis [Madruga et al., 2007]. These data suggest that a boosted PI-based second-line regimen would be effective in the majority of African patients who experience treatment failure while receiving NNRTI-based first-line ART. However, the generalisability of these data is limited as defining an optimized backbone is hazardous in LICs, where fewer ARVs are available and resistance testing is not widely available. Long-term data regarding second-line efficacy in resource-limited settings are not yet available and should be a subject for future research.

3.5 New antiretroviral drugs

New drugs within traditional drug classes and new drug-classes were developed over the last years. In western countries drugs such as boosted darunavir and etravirine as well as drug-classes such as fusion and integrase inhibitors, CCR5-receptor antagonists and maturation inhibitors expanded the antiretroviral arsenal. Long-term care for HIV-infected patients frequently demands switching to third- or consecutive lines of ART. Moreover, an individualised- rather than a protocol-based approach is increasingly being used. Viral characteristics, such as HIV-subtype and presence of drug-resistance mutations, as well as host characteristics such as medical history, organ functions and genetic background, all contribute to the efficacy and toxicity of the various ARVs. Most HIV-related pharmacological research was done in resource-rich settings, where Caucasian, male patients, infected with a subtype-B virus, predominate. Important differences exist between western and non-western countries regarding both these viral- as well as these host-characteristics. Even though the new ARVs will not shortly become available on a large-scale in LICs, it will be interesting to analyse what effects such drugs have in different ethnic populations and on various HIV-subtypes. Such research hopefully provides more insight in the dynamics between drugs, viruses and hosts and increases therapeutic options for all

HIV-infected individuals in the future. Moreover, expansion of the ARV armamentarium for second- and consecutive- lines of treatment is needed to ensure treatment success in the future.

3.6 Paediatric HIV care

Ninety percent of the 2.1 million HIV-infected children worldwide live in LICs. Until recently it was estimated that few vertically HIV-infected children survived beyond the age of five years. However, despite high mortality-rates in HIV-infected infants, a substantial increase of older survivors of mother-to-child transmission is visible in Africa [Ferrand et al., 2009]. Caring for small, HIV-infected children is associated with specific challenges, such as drug-administration problems and weight-based dosing. Later, during adolescence, an increased fear for stigma and loss of social acceptance may lead to a decreased adherence to treatment. Still, paediatric ART can result in virological and immunological benefits which are comparable to those observed among children in more developed settings [Ciaranello et al., 2009]. Unfortunately, despite optimistic, initial outcomes, long-term paediatric ART is associated with frequent virological failure [Barth et al. 2010c]. Similar to adult patients, most children were receiving NNRTI-based ART. Paediatric treatment outcomes may improve when PI-based regimens are used, which have a higher genetic barrier and are therefore somewhat more forgiving in case of sub-optimal treatment adherence. However, the effects of a long-term HIV infection and many years of ART on growth and development are not yet known. Simplifying treatment regimens and limiting side effects will be crucial to retain children in care and achieve good, long-term clinical outcomes.

4. Drug-resistance development

First-line ART failure is generally caused by poor adherence to the drugs. Various issues are linked to poor adherence. Drug toxicity is a major contributor, but other factors such as co-morbidities, insufficient drug supply, stigma, pill burden and traditional beliefs can play a role in drug-adherence. Contrasting initial fears, observed adherence rates in African ART programmes are good [Mills et al., 2006]. Still, around 15 percent of patients receiving first-line treatment in Sub-Saharan Africa experience virological failure within a few years after treatment initiation [Barth RE, 2010b].

In western guidelines it is recommended to perform resistance testing in case of virological failure in order to determine an optimal second-line regimen with a sufficiently high genetic barrier. Regular resistance testing is not feasible in most African clinics. In western countries, most HIV-infected individuals are infected with HIV-1, subtype B. This is in stark contrast with Sub-Saharan African countries, were less than one percent of patients subtype-B virus. Various non-B subtypes are prevalent, with subtype-C being most prevalent. Therefore, treatment outcome data and genotypic resistance data from western studies can not simply be extrapolated to African settings.

Available resistance data of people experiencing virological failure in LICs typically show (multiple) NNRTI-associated mutations and the lamivudine-associated M184V mutation [Barth RE, 2010b; Barth et al., 2008; Hoffmann et al., 2009; Marconi et al., 2008]. With such drug-resistance profiles a PI-based second-line regimen will generally be effective. Actual second-line treatment outcomes may however be less good. As in many HIV-treatment programmes in LICs regular HIV-RNA testing is not feasible, and due to the delay before immunological and clinical decline becomes apparent, there may be a large number of

people where virological failure remains unnoticed [Castelnuovo et al., 2009b; Kantor et al., 2009; Keiser et al., 2009; Reynolds et al., 2009b]. These people will continue their failing, first-line regimen. This is important, as a delay in treatment modification after virological failure is associated with an increased mortality [Petersen et al., 2008]. Moreover, an accumulation of drug-resistance mutations is observed in patients who continue first-line ARVs in spite of virological failure, limiting future treatment options [Cozzi-Lepri et al., 2007; Hoffmann et al., 2009; Reynolds et al., 2009a]. Empirically starting second-line ART in programmes with limited access to virological diagnostics, may therefore result in sub-optimal treatment outcomes, stressing the need for affordable, easy-access drug-resistance tests in LICs.

Drug-resistant HIV not only decreases the efficacy of new ART regimens in patients harbouring such a virus; transmission of resistant strains in the community may also limit first-line treatment outcomes of newly infected individuals [Barth et al., 2008; Kuritzkes et al., 2008; Wensing et al., 2005]. Fortunately, transmission of drug-resistant viruses is still limited in the African continent. Published primary resistance rates are generally well-below the WHO cut-off rate of five percent [Bartolo et al., 2009; Bussmann et al., 2005; Derache et al., 2008]. The prevalence of drug-resistant viruses will probably increase in LICs though, as ARVs become more widely available in those countries. Regular monitoring of primary resistance is needed to predict whether currently used treatment regimens will remain effective in the majority of patients.

5. Co-morbidities

Many other, both communicable and non-communicable, diseases can cause morbidity and mortality in HIV-infected individuals. Diagnosing and treating such co-morbidities are of utmost importance when caring for people with HIV. Below, a few of these diseases will be briefly addressed.

5.1 Tuberculosis

Concomitant with the HIV epidemic, South Africa has one of the worst TB epidemics of the world [Abdool Karim et al., 2009; WHO, 2009]. The HIV/TB co-infection rate is estimated to be as high as 70%, causing morbidity and mortality in many. However, making a definite TB diagnosis is hazardous, especially in HIV-infected individuals. In immuno-compromised patients, sputum-smear-negative and non-pulmonary TB are frequent, limiting the utility of commonly available TB diagnostics. Culturing mycobacterium tuberculosis, the golden standard when making a TB diagnosis, is often omitted due to the time and money needed for these tests. Therefore, there is a clear need for accurate, simple and low-cost diagnostic tests for the detection of TB infection.

The use of ART causes a great reduction in the risk of developing TB in the long term [Badri et al., 2002]. However, the incidence of TB increases soon after ART initiation, following the restoration of immune responses [Bonnet et al., 2006; Lawn et al., 2005; Moore et al., 2007]. As a result, TB is an important cause of the high mortality during the first months of ART, observed in many HIV treatment programmes [Brinkhof et al., 2007; Koenig et al., 2009; Lawn et al., 2008; Manabe et al., 2009].

The WHO declared that "urgent and extraordinary means" are needed in order to combat this massive disease burden, and it set targets for cure and case detection rates [WHO, 2009]. Unfortunately, in South Africa these targets are far from being met. Case detection rates are only 62% instead of the WHO minimum target of 70% and cure rates are only 58% instead of

the intended 85% [Abdool Karim et al., 2009]. These worrying figures are partly due to the expansion of multi- and even extensively- drug-resistant TB (MDR and XDR). Case-fatality rates are much higher in case of drug-resistant TB, compared with sensitive mycobacterial infections. Exogenous, nosocomial re-infections are thought to drive the spread of drug-resistant TB. Drug-susceptibility testing is needed to identify those in need of stricter isolation and broader anti-tuberculosis treatment regimens. However, susceptibility testing is currently only done in a subgroup of re-treatment cases and even if such testing is performed, it often takes long before results are available. The development of cheap, fast HIV-tests was an important contribution to the massive scaling up of HIV-care. Such easy-access tests are also needed to make a rapid TB diagnosis and to differentiate drug-resistant from normally susceptible infections [Lawn et al.]. Hopefully efforts to optimize diagnostic and treatment strategies, combined with a better integration of HIV- and TB-care will eventually result in a reversal of the TB epidemic.

5.2 Hepatitis

Apart from TB, hepatitis B (HBV) and C (HCV) co-infections are commonly observed in HIV-infected individuals. As ART roll-out continues, life expectancy of HIV-infected individuals in resource-limited countries improves. As a result, long-term effects of such hepatitis co-infections, like liver cirrhosis and hepato-cellular carcinomas, become more evident. HBV as well as HCV are highly prevalent in African, HIV-infected individuals (15% and 7% respectively', but there is a wide geographical variation in HBV and HCV prevalence [Barth et al. 2010a].

In western countries HIV infection is strongly associated with an increased incidence of both HBV and HCV [Burnett et al., 2005; Rockstroh et al., 2005; Thio, 2009]. This association is attributed to shared routes of transmission: mostly (homo)sexual contact in the case of HBV and intravenous drug use (IVDU) for hepatitis C [Cooper et al., 2009; Lavanchy, 2004; Modi and Feld, 2007]. In African countries HBV acquisition is assumed to occur during early childhood. As the route of HIV transmission in Africa is mainly via heterosexual contact, at a later point in life, it can be expected that the association between both infections is limited. However, reliable data on the mode and age of HBV acquisition amongst HIV-infected individuals in Africa are lacking. The predominant mode of HCV transmission in Africa is not yet established. However, IVDU seems to be less influential as in western countries [Cooper et al., 2009; Lavanchy, 2004; Modi and Feld, 2007]. Due to the different times and modes of transmission, the observed association between HIV and the hepatic viruses is less evident in Sub-Saharan Africa. Still, the burden of HIV/hepatitis co-infections in that region is high, as all these viruses are highly endemic. According to WHO estimates, 22.5 million HIV-infected people lived in Sub-Saharan Africa by the end of 2007 [WHO, 2007]. When geographical variations in HBV and HIV prevalence are not taken into account, an HBV prevalence of 15% would mean that 3.4 million HBV/HIV co-infected people live in this region.

HIV accelerates the progression of HBV and HCV related liver disease. Evidence that such co-infections are also associated with an increased mortality came available only recently [Chen et al., 2009; Nikolopoulos et al., 2009]. It is to be expected that HBV and HCV related cirrhosis and malignancies will become even more evident during coming years, as ART roll-out carries on and life-expectancy for HIV-individuals improves.

Knowledge on a patients' HBV/HCV status can help clinicians interpret clinical problems and lab results. More importantly, such information can guide decisions on which ARVs can

best be prescribed in co-infected patients. The vast majority of first-line ART regimens in Sub-Saharan Africa contain lamivudine. Lamivudine has long been approved for the treatment of chronic HBV. However, it has a poor resistance profile. Around half of HBV-isolates show drug-resistance mutations after 2-3 years of lamivudine use [Liaw et al., 2000; Lok et al., 2000]. Tenofovir is not yet widely available in Sub-Saharan Africa, but its use may increase during coming years. This nucleotide analogue has been approved for the treatment of HBV in 2008. Rates of HBV suppression in mono-infected patients are impressive and drug-resistance development seems to be limited [Marcellin et al., 2008]. Another problem regarding lamivudine use in HIV/HBV co-infected patients can arise when lamivudine is being stopped. A paradoxical HBV 'flare up' can occur, potentially causing liver tissue destruction [Lim et al., 2002].

Treating HCV infections is not feasible in most African settings due to the high costs and intensive monitoring associated with currently available therapies. Still, knowledge on a possible HCV co-infection is useful. Screening policies for liver cirrhosis and hepato-cellular carcinomas can be installed and the use of hepato-toxic agents can be minimized.

5.3 Non-communicable diseases

The unprecedented increase in ART roll-out which took place over the last decade shows what can be achieved with the joined efforts of international organisations, governments, non-governmental organisations and many enthusiastic, hard-working people. An extensive expansion of health care infrastructures was realized in many countries in order to reach and treat the millions of HIV-infected individuals. Large funds were made available to make ART free of charge for most patients. After being enrolled in an HIV-treatment programme, patients are frequently also provided with other medical care, like the diagnostics for and treatment of opportunistic infections. For HIV-negative persons on the other hand, medical care is frequently less readily available and costly. This may lead to disparities between individuals with HIV and those who are suffering from other (chronic) illnesses. Instead of increasing the gap between medical care that is available to HIV-infected and HIV-uninfected individuals, we should try to extend the benefits of the improved health care systems to other target groups. As in the established market economies, non-communicable disorders are the leading cause of death in adults in low- and middle-income countries. Ischemic heart disease and cerebrovascular accidents are the most frequent causes of death. Risk factors such as hypertension, diabetes, smoking and obesity are major contributors to this disease burden [Chopra et al., 2009; Gill et al., 2009; Lopez et al., 2006; Murray and Lopez, 1997; Sliwa and Mocumbi, 2009]. Sub-Saharan Africa includes countries with the highest non-communicable disease burden, such as South Africa. Poor people living in urban areas are affected most, but the burden is clearly rising in rural communities [Mayosi et al., 2009]. This rise is partly due to demographic changes; people grow older despite the negative effect of the HIV epidemic.

As ART roll-out continues, cardiovascular diseases will become even more evident due to a decline in HIV-related mortality. Moreover, an increased incidence of inflammatory circulatory disorders is observed in HIV-infected individuals and the use of PIs and certain NRTIs is associated with a greater risk of insulin resistance, lipodystrophy and dyslipidaemia [Friis-Moller et al., 2007; Grunfeld et al., 2009; Hsue et al., 2009]. Despite these worrying figures, attention for the prevention and treatment of non-communicable diseases in African countries has been limited because most efforts were directed at combating the

HIV and tuberculosis epidemics. However, there is a growing recognition that an integrated chronic care model is needed to combat both epidemics of communicable and non-communicable diseases in Sub-Saharan Africa. Surveillance, treatment and prevention strategies need to be improved [Unwin et al., 2001].

6. Finance

Over the last decade more funds have been raised to combat the HIV epidemic than have ever been made available for a single disease. The above described successes would never have been achieved without these funds. However, due to the number of HIV-infected people and the chronic nature of the disease, there remains a continued need for large amounts of money. Expansion of preventive strategies, earlier and wider access to ART, increased availability of laboratory testing, and improved health care facilities for both HIV-infected and HIV-uninfected individuals are all urgently needed, but costly. HIV-care is generally sponsor-based, making it sensitive to global economic instability. Currently, the economic crisis, and possibly donor fatigue, are negatively influencing the amount of money donors are willing to spend on the worldwide HIV epidemic [Ewing, 1990]. Therefore, using the available resources as efficiently as possible is of utmost importance. Prioritizing is needed when treatment capacity is limited, but leads to many difficult ethical and humanitarian dilemmas. Rather than considering the costs associated with expanding HIV care, we should consider the costs of not treating all HIV-infected individuals. A recent modelling study argues that by spending the available money wisely, but rapidly, eradication of AIDS will be feasible. Holding money in reserve now, could lead to extra, unnecessary infections and therefore extra costs in the future [Smith et al., 2009]. Moreover, the loss of large numbers of people who are in their working age and the resulting increase in HIV-related orphans has an enormous negative impact on economies and future generations. Therefore, continued attention and funds are still needed to control the HIV epidemic and to hopefully make HIV care more affordable in the future.

7. Conclusion

Since the start of the HIV epidemic, much progress has been made regarding global HIV-care. The joint efforts of people, organisations and governments around the world made it possible to reverse a previously fatal disease to a chronic condition and to prevent many from becoming newly infected. This is a great accomplishment. Still, the time to "sit back and relax" has by no means been reached. As in LICs large-scale ART has only been available for a couple of years, the long-term effects of HIV infections and their treatment in different groups of people are still unknown. Where initial programmes were mainly focussed on treating as many HIV-infected people as possible, future studies need to focus on the long-term care. There are important differences, both in host as in viral factors, between the western and African HIV epidemics. The long-term treatment effects, adverse events and viral resistance profiles in African ART programmes therefore need to be analyzed. In addition to the currently available strategies, new preventive methods and treatments are under development. Testing their efficacy and making them available in LICs should be another focus of future research. Moreover, by extending the focus beyond HIV-care and trying to improve the care for other important chronic diseases, HIV scale-up may generate substantial benefits for the broader health system in many countries.

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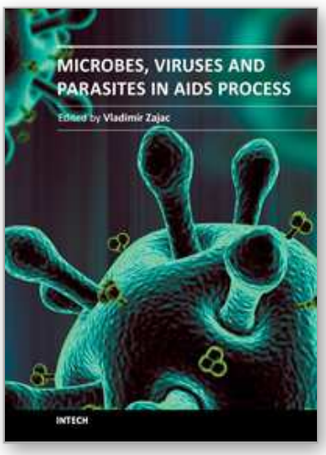

Microbes, Viruses and Parasites in AIDS Process

Edited by Prof. VladimÃr Zajac

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The main goal in compiling this book was to highlight the situation in Africa in terms of AIDS and opportunistic diseases.Â Several chapters reveal great poverty, an apocalyptic situation in many parts of Africa.Â Global migration of people resulted in their exposure to pathogens from all over the world. This fact has to be acknowledged and accepted as African reality. New, unconventional hypotheses, not determined by established dogmas, have been incorporated into the book, although they have not yet been sufficiently validated experimentally.Â It still applies that any dogma in any area of science, and medicine in particular, has and always will hinder progress. According to some biologists, in the future, AIDS is very likely to occur in a number of variations, as a direct result of the ongoing processes in the global human society. Thus, we urgently need a comprehensive solution for AIDS, in order to be ready to fight other, much more dangerous intruders.

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