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HIV Epidemiology and Prevention

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1. Introduction

Three decades after the discovery of the Human Immuno deficiency Virus (HIV) and its causal relationship with Acquired Immune Deficiency Syndrome (AIDS), HIV/AIDS continues to be a global burden, with more than 60 million people being infected resulting in approximately 25 million deaths. The devastating impact of the HIV/AIDS pandemic on morbidity and premature mortality on families, communities and societies is most noticeable in resource limited countries that bear the brunt of the disease burden.

By the mid-1990s, following the introduction and success of the life prolonging combination of antiretroviral (ARV) treatment (ART), also known as Highly Active Anti-Retroviral Therapy (HAART), transformed HIV-1 from being an "inherently untreatable" (Broder, 2010) infectious agent to one highly susceptible to a range of therapies. Through global solidarity, political will, effective government and private agency partnerships, ART has become increasing accessible in resource constrained settings, significantly reducing AIDS-related morbidity and mortality. Despite these major advances in the scale-up of ART provision, the continued spread of HIV remains a challenge in many resource-rich and poor countries, and preventing sexual transmission of HIV remains a public health priority.

A key lesson in terms of altering pandemic trajectories at a country level and globally has been the importance of understanding the local epidemic with regard to the virus, modes of transmission and populations most impacted. This will provide information to customize targeted interventions. Recent research on HIV prevention strategies highlights the increasing opportunities available and progress made to prevent HIV transmission, however, implementing these interventions remain a challenge.

This chapter reviews the complex diversity of the evolving HIV pandemic, and potential interventions, strategies and challenges in planning access to prevention programmes to alter the course of the disease worldwide.

2. Epidemiology of HIV/AIDS: Recent trends

Current estimates by the Joint United Nations Program on HIV/AIDS (UNAIDS) suggest a declining trend in the number of new infections due to a combination of factors,

including HIV prevention efforts and the natural course of the epidemic. By the end of 2009, globally an estimated 33.3 million (range 31.4 million–35.3 million) people were living with HIV, with 2.6 million (range 2.3 million–2.8 million) new HIV infections and 1.8 million (range 1.6 million–2.1 million) deaths from AIDS occurred. However, in several regions and countries new HIV infections increased by more than 25% (Eastern Europe and Central Asia) or has remained stable (Western, Central and North America). In some countries there is evidence of a resurgence of HIV in men who have sex with men (MSM), and high rates of HIV transmission continue to occur in networks of people who inject drugs through shared needles and their sexual partners. Worldwide majority of all new HIV infections occur in women and account for more than 45% in the 15–24 year age groups each year.

Sub-Saharan Africa is home to approximately 10% of the world's population, yet bears a disproportionate burden of the disease, accounting for 67% of the global HIV infections, with over 80% occurring in women. While there has been some decline in the recent number of new HIV infections, HIV incidence and mortality rates remain unacceptably high, with more than 75% of global AIDS related deaths occurring in this region. Despite the much later appearance of the epidemic in Asia, the region home to approximately 60% of the world's population, the epidemic patterns vary between and within countries. HIV prevalence is increasing in low-prevalence countries such as the Philippines, Bangladesh and Pakistan where injecting drug use (IDU) is the main mode of HIV transmission. In Thailand the prevalence is close to 1% and the epidemic appears to be stable, while in China five provinces account for more than 50% of infections. In India the prevalence has remained below 1% and remains concentrated in IDU's, sex workers and their clients. Although the numbers of new HIV infections are increasing in certain parts of South-East Asia, the national adult HIV prevalence is likely to mask growing local concentrated epidemics. In many eastern European countries and in central Asia, the number of HIV/AIDS cases is rapidly increasing, with an estimated 70% of those infected live in the Russian Federation. The trends in HIV infections in Latin America have changed little in the past decade, with the largest epidemic being in Brazil (adult prevalence 2%), which, due to widespread access to ART, has seen a decline in the number of deaths. Throughout North America, Western and Central Europe, the HIV epidemic has remained stable for several years, as access to life-prolonging ART has led to an increase in the number of people living with the disease. However, recent data suggests that new epidemics are emerging among young women 15 to 24 years of age and in minority ethnic groups. Of concern are the growing epidemics in the Oceania region, where the number of new infections has doubled, and over 70% of HIV infected people live in Papua New Guinea. In Australia and New Zealand, the HIV prevalence has remained below 1% and is concentrated among MSM. While the epidemic in the Caribbean region appears to have stabilized, the majority of people living with HIV are concentrated in the Dominican Republic and Haiti, with MSM accounting for more than 80% of all reported HIV cases. The epidemics in the Middle East and North Africa regions have not been well characterized, as there is a paucity of surveillance data, with adult HIV prevalence not exceeding 0.3%. Figure 1 shows the current worldwide burden of HIV infection (Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO). 2010).

Considerable progress has been made towards the Millennium Development Goal (MDG) 6, "to halt and begin to reverse the HIV epidemic" (United Nations Millennium Development

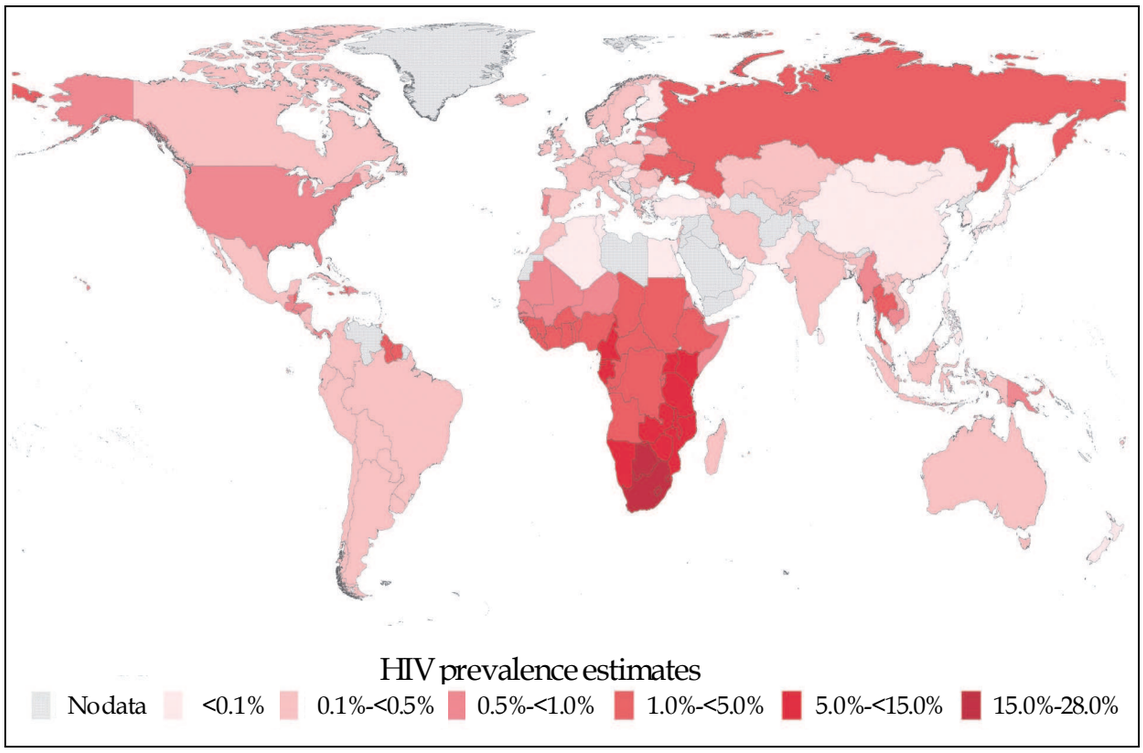

Fig. 1. Worldwide burden of HIV infection (Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO). 2010)

Goals., 2000) through the Declaration of Commitment made in the 2001 United Nations General Assembly Special Session on HIV/AIDS (UNGASS) where member states committed to enhance, co-ordinate and intensify regional, national and international efforts to comprehensively address the problem of HIV/AIDS in all its aspects (United Nations General Assembly., 2001). This commitment was intensified more recently through the 2006 United Nations Political Declaration on HIV/AIDS. Prevalence appears to have stabilized or show a downward trend in many countries, yet worldwide, HIV continues to disproportionately affect women and young girls. For example in southern Africa, where more women than men are living with HIV, young women aged 15–24 years are as much as eight times more likely than men to be HIV positive (Gouws, Stanecki, Lyerla, & Ghys, 2008). Therefore, any decline in new infections in young women in this age group will significantly impact the epidemic globally.

3. Know your HIV epidemiological typology and modes of transmission

The HIV epidemic has evolved differently around the world, and it is important to understand the evolving transmission dynamics at country, regional and local level to prioritize and tailor appropriate prevention interventions. Epidemics are highly dependent on when the virus was introduced into a community, the sexual networks, risk behaviours of partner change, concurrent or overlapping sexual relationships, bridging populations, mobile populations through migratory work systems and gender imbalances. In addition, poor infrastructure development, poorly skilled populations, poverty, widespread hunger

and social instability in many countries have impacted and aided the spread of HIV. The country level epidemics are described and classified by their current state, ranging from being low-level, to concentrated, then generalised and finally hyper-endemic generalised based on the HIV prevalence in different populations (Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO), 2007a).

Countries experiencing low-level epidemics are those where HIV has been prevalent for many years but is confined to most-at risk populations, often amongst individual with high risk behaviour in specific groups such as female sex workers (FSW), IDU and MSM. The sexual networks of risk in this epidemic state are not diffuse, with low levels of partner change or concurrent sexual relationships, or the virus may have been introduced only very recently. Generally, the HIV prevalence does not exceed 5% in any defined most-at-risk population and 1% in pregnant women, and this type of epidemic is seen in Senegal in West Africa and in parts of central Europe.

Concentrated epidemics are characterized by HIV spreading within a defined sub-population such as MSM, IDU or sex workers and their clients. HIV remains at high levels in these sub-populations and is not well established in the general population, suggesting active networks of risk are within a defined sub-population that do not bridge or cross into other populations. The disease burden and infection rates vary substantially between countries, and HIV prevalence is consistently above 5% in most-at risk populations, yet remains below 1% in pregnant women. Within these concentrated epidemics, the mode of transmission may change as epidemics within sub-populations continue. The epidemic in the United States of America, Canada, Central and South America, Europe, Australasia, China, many countries of South East Asia and parts of Africa (Ghana) represent this type of epidemic. Most countries have geographical and regional variations in their HIV epidemics and can experiences a mix of epidemics which evolve over time from low level epidemics to concentrated epidemics.

In generalized epidemics, such as in most countries in sub-Saharan African, HIV is firmly established in the general population and not dependent on the most-at-risk groups. The epidemic is sustained through heterosexual transmission; countries report an HIV prevalence of about 5% in adults and in excess of 5% among pregnant women with a concomitant epidemic of perinatally acquired infections. Southern Africa remains at the epicentre of the global AIDS epidemic and has the characteristic of a hyper-endemic generalized epidemic, with an adult HIV prevalence exceeding 15% in the general population [Swaziland (25.9%), Botswana (24.8%), Lesotho (23.6%), Mozambique (16.1%), South Africa (17.8%), Zambia (13.5%) and Zimbabwe (14.3%)] (Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO). 2010). New infection rates are higher than 5% per year despite high and increasing morbidity and mortality rates, with all sexually active persons having an elevated risk of acquiring HIV infection. These epidemics are driven through extensive heterosexual multiple concurrent partner relationships, specifically when young women have sexual relationships with men who are older through intergenerational or cross-generational relationships which often involves the exchange of goods or money through transactional sex.

4. Principles for HIV prevention

As the HIV epidemics within countries and regions may not be homogeneous in typology, may evolve over time from a low level scenario through concentrated and generalized

phases to a hyper-endemic scenario, or remain relatively stable or decline, the design of HIV programs must be tailored to shape the course of the epidemic. To ensure an effective national HIV prevention response, "strong, informed and committed leadership, coordination and accountability" are required to include the most vulnerable and to meaningfully include those living with HIV. UNAIDS guidelines encourage countries to "know your epidemic and your current response", which requires identifying the key drivers of the epidemic, focusing on the relationship between the epidemiology of HIV infection and the behaviours and social conditions that impede their ability to access, as well as to use HIV information and services. Knowledge of the epidemic provides the basis for determining the response, and enables countries to "match and prioritize your response" by identifying, selecting and funding those HIV prevention measures that are most appropriate and effective for the country in relation to its specific epidemic scenario. The key to this response must enable countries to "set ambitious, realistic and measurable prevention targets" in relation to the epidemic scenario, to synthesize essential prevention measures required to "tailor your prevention plans" and "utilize and analyse strategic information" to modify, enhance or strengthen the HIV prevention measures that are likely to produce the greatest impact in each setting by promoting access to HIV prevention, treatment, care and support.

5. Preventing sexual transmission of HIV

Despite the many diverse HIV epidemics globally, each with its own dynamic characteristic, young women continue to be at considerable risk of infection. Sexual transmission remains the primary route of infection worldwide, accounting for approximately 80% of all cases. Transmission occurs through any unprotected penetrative sex act where one partner is infected with HIV (discordant sex acts), with the risk of becoming infected being dependent on the background prevalence in the population, the number of concurrent partnerships, the frequency of change of sex partners, the frequency of unprotected sex acts, the type of sex act (receptive anal versus receptive vaginal), and the amount of virus (viral dose) present in the semen, vaginal, or cervical secretions of the infected partner. The viral dose is dependent on the stage of HIV infection, with individuals who have recently been infected having the highest virus load, followed by those with a concomitant sexually transmitted disease, followed by those with advancing HIV disease, having a high concentration of HIV receptor cells at the site of infection, which increases the risk of acquiring and transmitting HIV (Abu-Raddad & Longini, 2008; Gray, et al., 2001; Pettifor, Macphail, Rees, & Cohen, 2008; Pilcher, et al., 2007; Pilcher, et al., 2004; Quinn, et al., 2000).

In generalized hyper-endemic epidemics, HIV infection extends beyond discrete populations of MSM, IDU and sex workers; the background prevalence of HIV is a significant risk factor for HIV acquisition. The majority of HIV-infected individuals are unaware of their HIV status which remains a barrier for both treatment access and prevention. For many women, being married is the single biggest risk factor for HIV acquisition. Concurrent and multiple sexual partnerships, low condom use, low levels of male circumcision, early sexual debut, transactional sex, age disparate or intergenerational sex relationships, anal sex, non-injecting drug use, alcohol use, and sexual violence increase HIV risk disproportionately in women and help sustain high

rates of HIV infection in these settings. (Dunkle, et al., 2007; Harrison, Cleland, & Frohlich, 2008; Jewkes, et al., 2006; Kalichman, et al., 2007; Kenyon C & Badri M, 2009; Leclerc-Madlala, 2008; Lurie, Williams, & Gouws, 1997; A. E. Pettifor, van der Straten, Dunbar, Shiboski, & Padian, 2004; Sikweyiya & Jewkes, 2009; Van Tieua & Koblina, 2009; Zablotska, et al., 2009). To appreciate the complexities of HIV transmission, it is important to better understand individual behaviours and sexual networks within a broader context of political, economic, and social forces that enable or serve as barriers to HIV risk (Rothenberg 2009). While there are a number of issues that need to be addressed in order to prevent the spread of HIV infection, developing promising new preventative technologies could directly benefit young girls and women who account for more than 50% of new infections worldwide.

5.1 Health sector interventions

In many health care settings, HIV counselling and testing, peer education, treatment of sexually transmitted infections (STIs) as well as condom promotion and provision are delivered as integrated HIV prevention packages. Despite the 90% clinical effectiveness of preventing HIV transmission, the public health use of condoms is confined predominantly to FSW and MSM. Patterns of male condom use as a barrier method are heavily influenced by the form of partnerships. Condom use is generally highest in commercial sex work and lower in non-commercial and regular partnerships. In long-term or regular partnerships, condom use is often inconsistent and low among those at highest risk where the partner is not monogamous (Moyo, Levandowski, MacPhail, Rees, & Pettifor, 2008). In many relationships, women's inability to influence men reflects the fact that men usually dominate women's sexual lives and often impose whether intercourse will take place or not, and whether a condom will be used. As male condom use is largely dependent on male partners, the female condom, a female-initiated HIV prevention method if used correctly and consistently, can potentially help women to protect themselves from becoming infected with HIV. However, although the female condom allows partners to share the responsibility of condom use, it still requires some degree of male co-operation. As men are involved in sexual transmission of HIV either through heterosexual transmission or through MSM, men's behaviour is strongly influenced by concepts of masculinity. It is important that programs are designed to influence and persuade men to be responsible and protective to themselves and their partners.

The sexual transmission of HIV infection within partnerships seems to be facilitated by several STIs. Epidemiological studies suggest a synergistic bidirectional relationship between STIs and HIV. STIs in HIV-uninfected men and women increases their susceptibility to HIV infection and similarly in infected individuals with HIV and STIs there is enhanced shedding of HIV in genital secretions (Rottingen, Cameron, & Garnett, 2001). Thus far only one community based randomised trial conducted in Mwanza demonstrated the effectiveness of enhanced case detection and treatment of symptomatic curable STI's (chancroid, syphilis, gonorrhoea, chlamydial infection, and trichomoniasis) in primary health-care services to impact on HIV incidence. The Mwanza trial demonstrated a significant 42% reduction in HIV acquisition in intervention communities (Hayes, et al., 1995), while no effect of an STI intervention on HIV incidence was reported from other trials (Ghys, et al., 2001; Kamali, et al., 2002; Kaul, et al., 2004; Wawer, et al., 1998). The recently

reported trials on herpes simplex virus type 2 (HSV-2) suppressive therapy for preventing HIV acquisition also failed to demonstrate effectiveness (Celum, et al., 2008; Celum, et al., 2010; Watson-Jones, et al., 2008). While several factors may have contributed to these contrasting results, treatment of STIs remains a public health priority.

5.2 HIV counselling and testing

HIV counselling and testing (HCT) has been an important prevention tool, and has been hypothesized that knowing one's status allows positive people to protect others from being infected and those who are negative to protect themselves from infection (The Voluntary HIV-1 Counseling and Testing Efficacy Study Group., 2000). As HIV is predominantly transmitted sexually and linked to MSM's, it has been surrounded by stigma and discrimination. Paradoxically, HIV testing, counselling and social support has provided limited confidentiality to those accessing these services and testing positive. A major hurdle for HIV infected young women to access prevention of mother to child transmission services following HIV counselling and testing is fear of stigma, discrimination and violence, further stigmatizing this age group. More recent studies have demonstrated that lack of access to HIV counselling and testing services remains a significant barrier to expanding access to treatment, particularly in developing countries. Efforts are under way in many countries to enhance acceptability, increase uptake, widen accessibility and provide an entry point to care and support for HIV positive individuals. The innovative approaches of provider-initiated HCT in health care settings (Joint United Nations Programme on HIV and AIDS and World Health Organization., 2007), and the client-initiated community based approaches (Coates, Richter, & Caceres, 2008; Khumalo-Sakutukwa, et al., 2008) are likely to promote knowledge of HIV status fundamental to accessing treatment, preventing onward transmission and promoting prevention. Despite the expansion of services, knowledge of HIV status remains low.

5.3 Microbicides and Pre-exposure prophylaxis (PrEP)

Female-controlled methods of HIV prevention are urgently needed, as the only proven method of consistent male or female condom use is dependent on male co-operation and compliance. Research into the development of microbicides (gel or cream) that could be applied to the vagina without a partner knowing, and which would prevent HIV infection, has received unprecedented attention and support. The over 60 candidate microbicides in development and 11 clinical trials testing six non-virus specific products have produced disappointing results, with none demonstrating a protective effect for HIV. The six candidate microbicides include nonoxynol-9 (N9) (Van Damme, et al., 2002), SAVVY® (C31G; Cellegy Pharmaceuticals, USA) (Feldblum, et al., 2008; Peterson, et al., 2007), cellulose sulfate (CS) (Van Damme, et al., 2008), Carraguard® (PC-515; Clean Chemical Sweden) (Skoler-Karpoff, et al., 2008), PRO 2000 (Endo Pharamceuticals, USA) (Abdool Karim, et al., 2011; Kamali, et al., 2010) and BufferGel® (ReProtect LLC, USA)(Abdool Karim, et al., 2011).

Based on pre-clinical studies in different animal models, multiple studies have established tenofovir (antiretroviral, a nucleotide reverse transcriptase inhibitor) as a promising antiretroviral agent whether administered as pre-exposure or post-exposure prophylaxis to prevent simian immunodeficiency virus (SIV) (Tsai, et al., 2000; Van Rompay, 2010; Van

Rompay, et al., 2004), The recent major breakthrough and promising results from the CAPRISA 004 trial of 1% tenofovir gel used intravaginally to prevent HIV acquisition in women are welcomed (Abdool Karim, et al., 2010). The trial was the first phase 11B proof-of-concept study of an ARV in which 889 HIV uninfected; sexually active 18-40 year old, urban and rural women were randomly assigned to receive either placebo or tenofovir containing gel for the study duration. Women were prescribed to insert gel vaginally within 12 hours before and after having sex, and to use not more two gels within 24 hours. Of the 444 women on the placebo gel, 60 women became HIV infected while 38 of the 445 women in the tenofovir gel arm became HIV infected. The overall effectiveness was 39%, while 54% were protected when they adhered to using the gel as prescribed, covering more than 80% of sex acts, and 28% were protected when fewer than 50% of sex acts were covered. The added important finding of this trial was the absence of viral resistance, its safety and more importantly, the effectiveness of tenofovir gel to reduce the acquisition of HSV-2 infections by 51%. This finding is important as the risk of HIV acquisition increases to a large extent in women who are HSV-2 infected (Tobian & Quinn, 2009; Wald & Link, 2002).

Shortly after the release of the CAPRISA 004 trial results, the iPrEx (Pre-exposure Prophylaxis Initiative) trial demonstrated a 44% protection against HIV acquisition among MSM following the daily single oral dose of the ARV drug of Truvada® which contains two drugs : tenofovir disoproxil fumarate (TDF-300 mg) and emtricitabine (FTC-200 mg) (Grant, et al., 2010). The iPrEx study was a double-blind, placebo-controlled, Phase III clinical trial which enrolled 2,499 HIV-negative male volunteers and took place at 11 research sites in Brazil, Ecuador, Peru, South Africa, Thailand and the United States. There were 64 HIV infections among the 1,248 participants who received a placebo pill, while 36 HIV infections among those who received Truvada®. Among participants who used the pill more than 90 percent of days, protection against HIV acquisition was over 72%. However, the iPrEX study found no evidence that Truvada® taken orally provided protection against HSV-2 infection.

The success of these two trials provides growing evidence of the potential of ARV's to prevent sexual transmission of HIV. The efficacy and safety of ARV's are being tested in several oral and topical PrEP clinical trials. The FEM PrEP trial tested a daily single oral dose of Truvada® for heterosexual HIV prevention in 3900 high risk HIV uninfected women, 18-35 years of age in Kenya, Malawi, Tanzania, Zambia and South Africa. However, an interim review of the results of the FEM PrEP trial has established that Truvada® tablets taken orally was not able to demonstrate a protective effect in women against HIV infection, thus Truvada® may not be as effective in preventing HIV in women compared to its proven effectiveness in preventing HIV infection in MSM.

The Centre for Disease Control (CDC) BangkokTenofovir Study is testing the daily single oral dose of tenofovir in approximately 2400 HIV uninfected IDU in Thailand. Despite the disappointing FEM PrEP trial results, the CDC TDF2 PrEP study, a randomised, placebo controlled trial examined the safety and effectiveness of a daily single oral dose of Truvada® for reducing the risk of HIV acquisition among 1200 heterosexual men and women at two sites in Botswana. The study enrolled approximately 1200 participants and randomly assigned to one of two arms: 601 were assigned to take Truvada® tablet and 599 were assigned to receive a placebo. In the primary trial analysis there were nine HIV infections among the participants assigned to Truvada® compared to 24 infections among those

assigned to placebo, translating to a 62.6% (95% CI, 21.5 to 83.4; P= 0.0133) reduction in the risk of HIV infection among those receiving Truvada® .

Similarly the University of Washington 's Partners PrEP Study was a randomised, placebo controlled trial of daily single oral dose of tenofovir or Truvada® for the prevention of HIV-1 acquisition among HIV-1 seronegative partners in heterosexual HIV-1 sero-discordant partnerships. In the 4758 sero-discordant heterosexual couples in Kenya and Uganda, a total of 78 HIV infections occurred in the study: 18 among those assigned to tenofovir, 13 among those assigned to Truvada® , and 47 among those assigned to the placebo. Thus, those who received tenofovir had an average of 62% fewer HIV infections (95% CI 34 to 78%, P=0.0003) and those who received Truvada® had 73% fewer HIV infections (95% CI 49 to 85%, P<0.0001) than those who received placebo.

In 5029 sexually active, HIV uninfected women, 18-40 years of age in Malawi, Zambia, Zimbabwe, Uganda and South Africa the VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial is not only testing the daily single oral dose of tenofovir or Truvada® but also the vaginal tenofovir gel formulation. The trial design is important for determining how each product works compared to its control and which approach women may prefer. The trial is expected to complete follow-up in June 2012, by which time women would have used the assigned allocation for at least one year and some for nearly three years. The trial results are expected to be available in early 2013. More importantly, the development of HIV prevention products in the form of vaginal rings and injections may provide alternate modes of delivery possibly providing protection for longer duration. The planned Phase III Dapivirine ring study will expand the spectrum of ARV's available, with an alternate delivery mode for HIV prevention. The diverse populations, including heterosexual men and women in the ongoing clinical trials, would provide further evidence for HIV protection in different at-risk groups, although a key question to be addressed is whether the optimal drug level would be achieved if ARV's taken orally or inserted vaginally to provide maximum protection .

Both tenofovir and Truvada® are approved by the United States Food and Drug Administration (FDA) to treat HIV infection, and following long-term use, there have been no safety concerns. More importantly, these ARV microbicides provide hope to millions of women, and enables them to take responsibility and initiate its use as a female-controlled method to protect them from acquiring HIV. Adapting different forms of ARV's for HIV prevention, whether taken orally or inserted vaginally, either daily or coitally, has a great potential to transform the global response to the HIV/AIDS epidemic. The confirmation of these innovative scientific approaches from the proof-of-concept trials using ARVs for HIV prevention, suggest that new HIV prevention tools are attainable, but need to be easily accessible and affordable to potentially alter the epidemic trajectory which remains a global public health priority.

5.4 Medical male circumcision

The biological plausibility that HIV-1 targets cells in the inner mucosal surface of the male human foreskin which makes it highly susceptible to HIV infection has been tested through three randomized controlled trials. To evaluate the effect of medical male circumcision (MMC), i.e. partial or complete surgical removal of the foreskin on HIV prevention, the trials enrolled more than 10,000 HIV uninfected men from South Africa (Auvert, et al., 2005),

Kenya (Bailey, et al., 2007), and Uganda (Gray, et al., 2007). After 21 to 24 months of follow-up, all three trials demonstrated that MMC significantly decreased male heterosexual HIV acquisition by 41% to 66%, despite differences in age eligibility criteria, urban or rural settings, and surgical procedure (Auvert, et al., 2005; Bailey, et al., 2007; Gray, et al., 2007; Siegfried, Muller, Deeks, & Volmink, 2009).

Based on the compelling evidence from clinical trials and modelling of data (Hallett, et al., 2008; Williams, et al., 2006), UNAIDS and WHO have recommended that MMC be provided as an important intervention to reduce heterosexually acquired HIV in men, and that it be part of a comprehensive HIV prevention package which includes HIV testing and counselling services, treatment for STIs, male and female condom provision (Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO), 2007b).

In countries with generalised heterosexual HIV epidemics with high incidence rates, male circumcision rates are generally low, and for any significant public health benefit to be achieved, urgent scale up of MMC services should be considered (Lissouba, et al., 2010). A rapid public health impact would be achieved if MMC services are prioritised to age groups at highest risk of acquiring HIV. Nevertheless, providing MMC services to younger age groups will also have public health impact over the longer term. In countries with concentrated HIV epidemics, specific high risk populations of IDU's and MSM should be targeted to achieve an individual benefit for men at high risk of sexually acquired infection. While the scale-up of MMC programmes has the potential to lower HIV prevalence among the male population, in the long term women would benefit from reducing their risk of exposure.

Mathematical modelling suggests that in high burden countries in sub-Saharan Africa, with maximum coverage of male circumcision over a ten year period, it could avert 2 million new HIV-infections and 0.3 million deaths. In the 10 years thereafter, it could avert a further 3.7 million new infections and 2.7 million deaths, demonstrating the substantial public health benefits of male circumcision to lessen the transmission of HIV (Williams, et al., 2006).

Many sub-Saharan African countries have begun taking steps to increase the availability of MMC services, with set targets of maximum coverage to be achieved over the next five years despite the concerns of risk compensation, the challenges of cultural and social acceptability, limited financial and human resources, poor infrastructure and systems for monitoring and evaluating circumcision programmes (Kim & Goldstein, 2009; Weiss, Dickson, Agot, & Hankins, 2010). Additionally, more research is needed to determine the side effects of poorly performed circumcision with a risk HIV acquisition from poorly healed procedures, serious bleeding, risk of cross infection and damage to the penis (Lagarde, Taljaard, Puren, & Auvert, 2009; Schackman, 2010). As MMC provides partial protection, such programmes must be part of the comprehensive HIV prevention package (Hallett, et al., 2008; Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO), 2007b).

5.5 Antiretroviral treatment for HIV prevention

The transmission probability of HIV is dependent on the viral load, and there is a substantial reduction in HIV viral load following ART initiation, with simultaneous improvement in the general health of the person being treated. Increasing evidence from several studies suggest

that following the introduction of ART, transmission of HIV declines at the individual level. Amongst IDU's on ART in Vancouver, British Columbia, a decrease in the median plasma HIV-1 RNA concentration correlated with a decline in the incidence of HIV-1 infection. In a cohort study, HIV-1 transmission was 92% lower among couples in whom the index partner was taking ART (Donnell, et al., 2010). Extensive experience on the role of ART has been amongst pregnant and breastfeeding HIV positive women, with maternal ART having been highly successful as a prevention strategy for lowering the risk of mother to child transmission. Ongoing studies among sero-discordant couples will provide evidence of ART to lower the viral load and decreasing the risk of HIV transmission among adults.

The potential impact of ART to significantly impact on new HIV infection rates has recently been modelled on data from South Africa. Mathematical modelling suggests that wider HIV testing, and immediate ART for those testing positive, will significantly impact on new infection rates (Granich, Gilks, Dye, De Cock, & Williams, 2009). While the model assumes that individuals will test annually for HIV, persons testing positive, commencing ART immediately and maintain it for life will significantly reduce the new infection from 17 per 100 people per year (Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO), 2008) to 1 per 1000 people per year over the next 10 years, leading to eventual elimination of the epidemic. The model however, does not include the timing between infection, diagnosis and the introduction of ART, the acceptability of HCT, the need for high adherence to ART, risk behaviours of people undergoing treatment, as well as low level of transmission and an emerging drug-resistant virus. The risk of HIV transmission is generally highest during acute infection and the later stages of infection, providing some indication of where treatment might have its biggest prevention effect, thereby fitting into a comprehensive prevention approach. While the model is optimistic, it may be unattainable in real-world settings, as the effectiveness of ART, behavioural risk factors, HIV testing coverage, reluctance to commence ART for fear of stigma and discrimination and epidemiological scenario could have a major influence on the overall impact of HIV testing and treatment programs. Furthermore, more than 50% of HIV infected persons worldwide are unaware of their HIV status, and these figures are much higher in high burden countries. In many resource-poor countries, the existing strain on health care services is a major obstacle to initiation of ART, while in many well resourced countries, the HIV-linkage to care and treatment cascade dramatically declines, with many individuals requiring ART not being on treatment. Nevertheless there are numerous programmatic issues that need addressing prior to implementation of the wider HIV testing and immediate ART for those testing positive strategy. Research on each component will guide the programmes roll-out including providing evidence of the risk and benefits of early ART to individuals.

The most convincing results and significant findings of HIV treatment as prevention come from the HPTN 052 study which took place at 13 sites in Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, the United States and Zimbabwe. The randomised controlled trial enrolled 1,763 serodiscordant couples to test the effectiveness of currently licensed regimens of ART whether delivered early or delayed to reduce the risk of HIV transmission. At the time of enrolment, the HIV-infected partners (890 men, 873 women) had a median CD4+ T-cell count of 436 cells/mm^3, ranging from 350 and 550 cells per mm^3, while the HIV-uninfected partners tested negative for the virus. Participating couples were randomly assigned to one of two treatment arms. In the first group, the HIV-infected partners immediately began taking a combination of three ARV drugs. In the second group, the HIV-infected partners delayed taking ARV drugs until their CD4+ T-cell counts fell

below 250 cells/mm^3, or an AIDS-related illness as defined by World Health Organization guidelines occurred. Following a scheduled interim review of the study's safety and effectiveness data by the independent data and safety monitoring board (DSMB), the DSMB found that 28 of the HIV infections were linked through genetic testing to the HIV-infected partner as the source of infection. Of the 28 cases of linked HIV infection that occurred, 27 infections were among the 877 couples in which the HIV-infected partner delayed antiretroviral treatment. Only one case of HIV infection occurred among the 886 couples in which the HIV-infected partner began immediate antiretroviral treatment. This means that earlier initiation of ARV drugs led to a 96% reduction in HIV transmission to the HIV-uninfected partner ($P \leq 0.0001$). The added therapeutic benefit was the decline in the morbidity and mortality events; 40 events occurred in the early treatment arm compared to the 65 in the delayed treatment arm. There were 17 cases of extrapulmonary tuberculosis among HIV-infected participants in the delayed treatment arm compared with three cases in the early treatment arm ($P=0.0013$). There were 23 deaths during the study: 10 in the early treatment group and 13 in the delayed treatment group, a difference that did not reach statistical significance (National Institute of Allergy and Infectious Diseases., 2011).

While the initial WHO treatment guidelines of November 2003 recommended that anyone with advanced clinical HIV disease or those with CD4+ T-cell counts less than 200 cells/mm^3 begin ART, the follow-up revision over time recommended that ART be considered between 200 and 350 cells/mm^3. The most recent guidelines of November 2009 recommend the initiation of ART in all patients who have a CD4+ T-cell count of less than 350 cells/mm^3, irrespective of clinical symptoms. Though several countries have adopted the new guidelines, most have not primarily due to cost constraints and a lack of drug supply (World Health Organization., 2009).

If ART is to be considered as part of the HIV prevention program, programmatic scaling up of services will be required. Identifying appropriate target population; educating health workers; a wider availability of ART; regular HCT services; education and counselling of all people who test positive for HIV are key to ART initiation. Adherence counselling for people who agree to treatment; and regular follow-up, including ART safety assessment, ongoing adherence counselling, ongoing risk behaviour counselling, and testing for viral load rebounds and resistant virus are vital to sustaining the programme. While the roll-out and maintenance of such programmes pose numerous challenges, these are highly dependent on the commitment of ministries of health, donors, provider organizations and community groups. Preliminary studies from Côte d'Ivoire, San Francisco, Spain, and Taiwan, indicate that wider treatment is associated with fewer new HIV infections where ART-as-prevention occurs. In developing countries, expanding HCT services are offered by mobile testing units, mainly as part of provider initiated routine health care services, as an opportunity to rapidly identify persons to be linked to care and ART as prevention. The scale-up of ART provision requires critical evaluation to expand the evidence base. More data are needed through monitoring and evaluation that ART provides potential gains in preventing new HIV infections.

5.6 Behaviour change programmes for HIV prevention

Population based surveys have shown that young people 15 to 24 years of age are at a considerable risk for HIV acquisition, and account for almost 50% of new HIV infections worldwide. Early age of sexual debut, inconsistent or incorrect use of condoms, and

experimentation with alcohol and other substances, multiple, frequent and concurrent sexual partners significantly increase the risk of HIV acquisition.

To reduce the incidence of HIV, behavioural change interventions have been developed and implemented to reduce sexual risk (Coates, et al., 2008). These approaches include broad and diffused dissemination of factual information about HIV, frank discussions about condom use, and small-group interventions following interaction and role playing to enhance motivation and relevant knowledge and skills. School based HIV intervention programmes generally provide young learners with basic knowledge and are limited to being informational on how to prevent being infected. In a recent meta-analysis of sexual risk reduction interventions that have been successful at modifying behaviours more broadly delaying sexual debut, increasing condom use, abstinence or reducing or delaying frequencies of penetrative sex, and increasing skills to negotiate safer sex and acquire condoms have shown to be effective. Although intervention success varied across studies, the benefits were evidence sustained for up to three years post intervention, across gender and geographic region (Johnson, Scott-Sheldon, Huedo-Medina, & Carey, 2011). HIV intervention programmes amongst couples and families attempt to promote risk reduction through innovative strategies that include motivational behaviour change.

Behavioural science theories of using informational, motivational, and skills-based content to deliver interventions confirm that the efficacy of behavioural strategies together with motivational training providing greater condom skills training thereby encouraging condom use, and were more successful at decreasing the frequency of sex in younger rather than older adolescents. Effective behaviour change programs with comprehensive information on reducing HIV risk must be designed, tailored and implemented with informational, motivational, and skills-based content. They should be customised to address the needs and values of the groups they are designed to reach which will make them more likely to be effective at preventing HIV acquisition.

5.7 Structural interventions for HIV prevention

Insights into the variation in levels of risk in populations, as well as the biological and socioeconomic factors, are key to understanding risk of HIV acquisition and the speed at which HIV spreads through a population. This is dependent on a combination of structural, social, and political factors that shape behaviour, vulnerability, and risk. Sexual and ethnic practices, marginalised populations, women's status, restrictive national policies, restricted access to health care, fear of stigma and discrimination are important structural 'drivers', increasing vulnerability and contributing to HIV transmission. In many countries, HIV prevention efforts have not succeeded, as the underlying social and structural drivers of HIV risk and vulnerability have not been addressed.

Stigma and discrimination, gender inequalities, gender-based violence, human rights violations, mobility and economic power are the major structural drivers that hamper HIV prevention efforts and impede progress towards universal access to prevention and treatment programmes. HIV prevention efforts need to be adapted to change the root causes or structures that affect individual risk and vulnerability to HIV, ensuring that resources are targeted where they could have the greatest impact. While in many settings, structural interventions have addressed access to health care, sexuality and gender relations, stigma and discrimination; these have not been adequately evaluated at the programmatic level.

6. Combination HIV prevention programmes

The diversity and complexity of epidemics that make up the HIV pandemic underscores the importance of a diverse set of responses rather than a single solution for all settings. The UNAIDS "know your epidemic, know your response" provides a strategic, intensified framework for understanding the local epidemic in terms of prevalence and what is contributing to its spread (Wilson & Halperin, 2008). The proficient and competent planning of effective customized HIV prevention programs and monitoring their impact relies on strong health information systems as well as good local and national surveillance. The exact mix of HIV prevention, treatment, care, support strategies, and structural interventions is determined by this data (Horton & Das, 2008).

While several HIV prevention interventions appear promising with mathematical modelling providing further optism for the intervention, no single intervention is likely to be sufficient to prevent transmission of HIV on a global scale. Each intervention has its strengths and limitations, yet the current HIV prevention landscape consists of several important but partially effective interventions, none having been shown to be fully protective. The appropriate mix for each epidemic, to identify the target populations and establish what coverage and saturation levels are required remain challenges for effective approaches to alter the current epidemic trajectories The role of combination prevention programmes includes multi-level and multi-component interventions that incorporate biomedical, behavioural, and structural approaches which are considered highly active HIV prevention strategies and has been gaining increasing attention (figure 2).

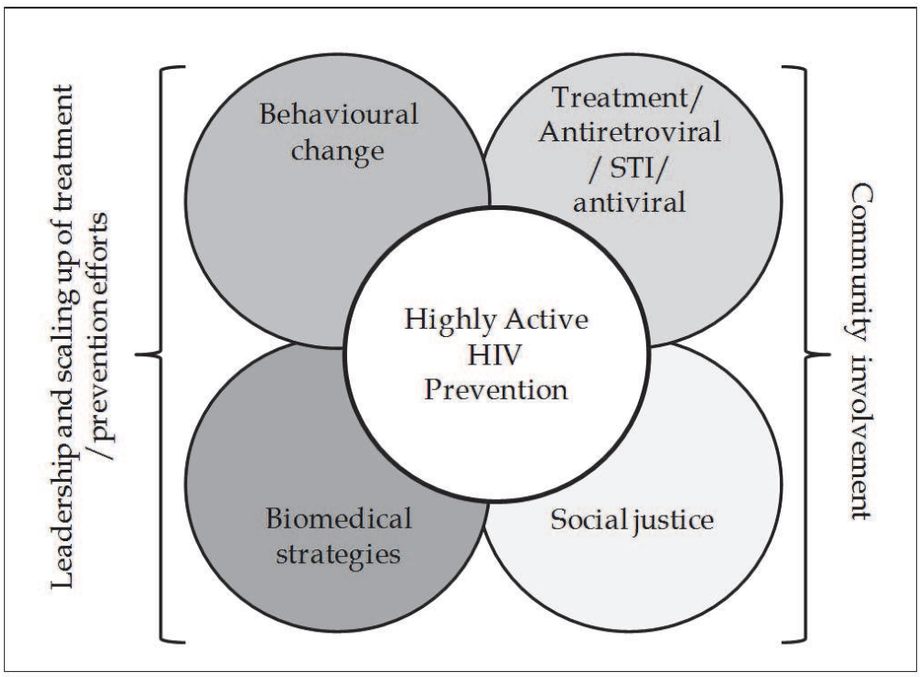

Fig. 2. Highly active HIV prevention Programme (Coates, et al., 2008)

The multilevel approach of combination behaviour change interventions is included into the HCT programme. The programmes are designed to include a range of activities to

encourage people to reduce their risk of being infected with HIV and to increase their protective behaviour. The approach aims to delay sexual debut, reduce sexual partnerships, reduce age-disparate relationships, encourage mutual monogamy, promote correct and consistent condom use, and increase the frequency of HCT. The messaging at different levels is to promote individual behaviour change and to encourage families, communities and social networks to adopt and maintain healthy norms and a supportive environment. In this context, at the individual level, educational, skills building and counselling can be delivered through small groups or schools-based HIV prevention programmes, and while these may be informational, they should be followed up with motivational skills-based programmes. Among couples, the HCT programme attempts to motivate behaviour change within primary and secondary relationships, and to focus on factors that are critical drivers of the epidemic. Concordant HIV positive couples have the advantage of joint referral for care, support and treatment. HCT, through a family-centred approach, has the advantage of easy access, reduces stigma and facilitating disclosure.

Behaviour change can be facilitated through education programmes delivered by peer groups, community leadership or through networks. Involving peers groups in vulnerable populations of FSW, MSM, IDU, high risk men at truck stops and transport workers has been effective in increasing condom use and reducing STIs. Peer education programmes have been highly successful in increasing condom use among secondary school students. The involvement of community leaders to initiate HIV prevention and risk reduction messages, and to sustain risk reduction conversations, has been an innovative method of diffusing information through communities. Network-based interventions are particularly important in disseminating HIV risk reduction messages, as social networks have played a role in the transmission of HIV. Intervention information delivered through workplace programmes not only provide an opportunity to reach large numbers of often high risk individuals, but take advantage of motivational approaches and peer network support.

In the absence of an HIV vaccine, recent evidence from biomedical interventions appears to be promising, although the levels of evidence have been inconsistent. While male and female condoms, if used correctly and consistently, have proven to be very effective in blocking HIV transmission during sexual intercourse, the challenges of access, availability, lack of negotiating skills, co-operation of male partner and gender related violence have been major obstacles to their use. Despite their ability to prevent transmission of HIV by more than 80%, there has been no impact on HIV incidence rates. The inconclusive results from the STI treatment trials on HIV acquisition make them difficult to interpret and to translate from research to policy. However, treatment of STIs remains an important public health benefit. The results from the three randomised trials on MMC, demonstrating the protective effect against HIV acquisition among men, provides sufficient available evidence to consider it as a public health intervention and calls for the its urgent scale up.

The two trials of topical and oral antiretroviral compounds demonstrate the potential of methods that could be used for protection from HIV acquisition during sexual intercourse. However, research on biomedical interventions poses formidable challenges and concerns with implementation; product adherence and the possibility of sexual disinhibition. While expanding ART for HIV infected individuals to reduce infectiousness, expanding the wider HIV testing, and immediate ART for those testing positive strategy could have a major impact on HIV transmission and HIV-1 incidence. Nevertheless, strengthening and expanding the HIV treatment programme is expected to have substantial benefits in reducing morbidity, mortality and infectiousness.

In countries where HIV prevalence remain disturbingly high, there have been calls for prevention programmes to fully address social and economic factors that increase vulnerability, and to focus on high impact interventions. Currently, there are no research studies which best address the role of combination HIV prevention programmes to determine the appropriate mix of interventions. At the individual level, it is not clear whether there might be personal preferences for a particular intervention, whether choices might be available, individuals may require customised risk reduction options or the intervention may need to be tailored to different times in their lives. Even more difficult is the role of health care planners who have difficulty in prioritising interventions and whether to target specific groups or the general population, and then implementing those programmes.

Within the context of a combination HIV prevention strategies, structural approaches that address social, economic, and political factors are deeply entrenched and difficult to change. However, interventions to combat gender violence, gender or income inequality and the social marginalisation of risk groups are long-term intervention initiatives that need to be supported through community and leadership involvement within the broader economic and social development. Structural interventions of facilitating microcredit programmes, involving women in opportunities to improve household economic wellbeing, their social capital, and reduce their vulnerability to intimate partner violence and therefore to HIV. Furthermore, attempts to address structural factors to reduce HIV risk are promoted through partnerships with non-governmental organisations, community groups and government agencies, but their value has been difficult to measure. Access to broader family planning and reproductive health care services may further empower women to take control of their live and reduce their vulnerability to HIV.

7. Conclusions

HIV prevention interventions need to be appropriate to the epidemic context and to address the right population groups with co-ordinated evidence and informed strategies that work toward shared prevention goals. This means prioritising scale-up, quality delivery and close monitoring and evaluation of prevention strategies of those that have the best chance of success within the background on the epidemic scenario. Combination HIV prevention programmes need to include strategies that address socio-cultural and behavioural communication issues relating to sexual partnerships. They also need to provide safe biomedical interventions for MMC as well as topical microbicides and PrEP within the context of wider sexual and reproductive health services. This needs to include strategic condom programming, risk perceptions and awareness integrated through easily and widely available HCT services to ensure that the majority of person in need of treatment are supported and rapidly initiated on ART for maximum coverage. Optimistically, with an integrated combined response of HIV treatment and prevention, the benefits are expected to be substantial, particularly in high burden settings such as sub-Saharan Africa (figure 3) (Salomon, et al., 2005). An impact on HIV acquisition in a region with the highest burden of infection will impact on the disease globally. As agreed by the member states at the United Nations General Assembly Special Session on HIV/AIDS, countries need to continue with their efforts and scale up towards the goal of "universal access to comprehensive prevention

programmes, treatment, care and support" which complement the United Nations Millennium Development Goals to reduce child mortality, improve maternal health and combat HIV/AIDS, malaria and other major diseases.

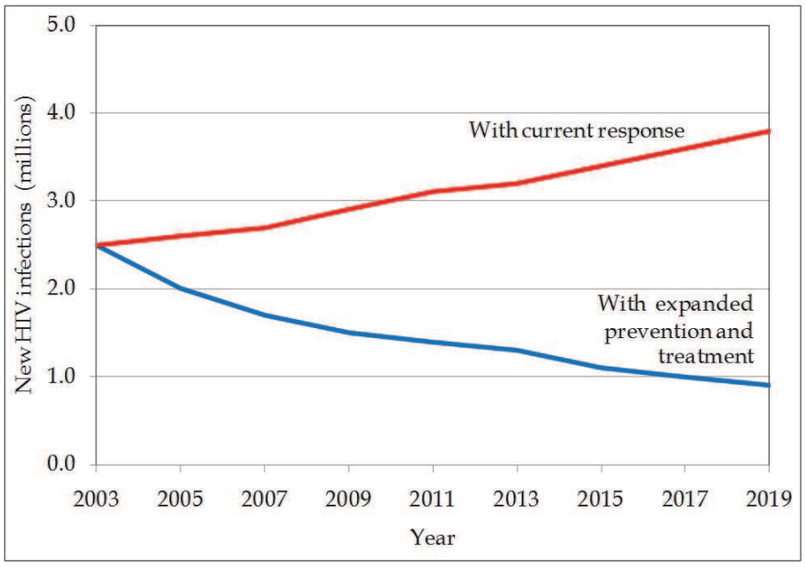

Fig. 3. Impact of treatment and prevention on new HIV infections in Africa (Salomon, et al., 2005).

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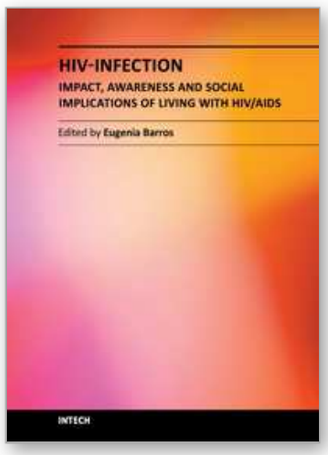

HIV-infection - Impact, Awareness and Social Implications of living with HIV/AIDS

Edited by Dr. Eugenia Barros

ISBN 978-953-307-343-9
Hard cover, 336 pages
Publisher InTech
Published online 26, October, 2011
Published in print edition October, 2011

The past few decades have seen the escalation of HIV-infections and the 'frantic' search for new drugs to treat the millions of people that live with HIV-AIDS. However because HIV-AIDS cannot be cured, but only controlled with drugs, and the Antiretroviral (ARV) treatment itself results in some undesirable conditions, it is important to generate wider awareness of the plight of people living with this condition. This book attempts to provide information of the initiatives that have been used, successfully or unsuccessfully, to both prevent and combat this 'pandemic' taking into consideration the social, economic, cultural and educational aspects that involve individuals, communities and the countries affected.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Ayesha B.M. Kharsany and Quarraisha Abdool Karim (2011). HIV Epidemiology and Prevention, HIV-infection - Impact, Awareness and Social Implications of living with HIV/AIDS, Dr. Eugenia Barros (Ed.), ISBN: 978-953-307-343-9, InTech, Available from: http://www.intechopen.com/books/hiv-infection-impact-awareness-and-social-implications-of-living-with-hiv-aids/hiv-epidemiology-and-prevention

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