

Biomedical Strategies for Human Immunodeficiency Virus (HIV) Prevention? A New Paradigm

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Abstract

Introduction: This article presents recent developments in biomedical interventions for prevention of sexual transmission of the human immunodeficiency virus (HIV) infection. **Materials and Methods:** A review of results from randomised clinical trials on the use of antiretroviral (ARV) medications and other biomedical methods to prevent the transmission and acquisition of HIV infection. **Results:** Pre-exposure prophylaxis (PrEP) refers to the provision of ARV medications to uninfected persons at high risk of HIV infection either in the form of topical agents, e.g. vaginal microbicide gels, or orally administered tablets. The Caprissa study demonstrated the efficacy of vaginal microbicides, the Vaginal and Oral Interventions to Control the Epidemic (VOICE) study however was not able to confirm these results. Oral PrEP was found to be efficacious in the iPrEx study on men who have sex with men (MSM), and among heterosexual couples in the Partners-PrEP and the TDF2 studies in Africa. The HPTN 052 trial demonstrated that the provision of early ARV treatment was able to prevent transmission of HIV by 92% compared with delayed treatment. This has led to enthusiasm to roll out treatment as prevention (TasP) programmes. Encouraging results from studies on male circumcision to prevent HIV acquisition have resulted in several implementation projects in Africa. Another encouraging result has been the success, albeit modest, of the prime-boost combination RV144 vaccine trial in Thailand. **Conclusion:** New advances in prevention strategies are urgently needed to slow down the HIV pandemic. Recent developments particularly in the form of PrEP and TasP have given new hope that we will be able to achieve this goal.

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Introduction

The first 30 years of the human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) pandemic will be remembered by the way individuals, communities, nations and organisations rallied to put an end the relentless spread of the infection and the death and suffering that it brought. Soon after it was described in gay communities in 1981 in the United States (US) and other parts of the developed world, epidemiologists suspected that the causative agent was likely to be spread through sexual intercourse. Reports of cases among heterosexuals in Africa lent credence to this hypothesis. The finding of AIDS among recipients of blood and blood products, among intravenous drug users and paediatric infections pointed to blood borne spread. Much has been accomplished in these 30 years, including the discovery of the causative agent, development of diagnostic assays, elucidation of the life cycle of HIV, and understanding the pathogenesis of the HIV infection and AIDS.

Behavioural Strategies

It became clear early on that major changes in sexual behaviour especially among groups with the highest prevalence of HIV infection were needed to stop the sexual spread of HIV. Promotion of safer sex strategies was introduced everywhere, especially targeting most at risk communities. Behavioural change strategies included sexual abstinence, entering into mutual monogamous relationships, delaying sexual debut, reducing the number of sexual partners, avoiding sex with persons who may have many other sexual partners, and the correct and consistent use of condoms. One hundred percent condom use campaigns in particular were successful in several countries and reduced HIV infection among sex workers, for example in Thailand, Cambodia¹ and Singapore.²

Behavioural interventions to reduce the spread of HIV have led to the decline in the incidence of new HIV infections in most parts of the world. In its 2010 report UNAIDS

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estimated that since 1999, the year when the epidemic peaked globally, the incidence of new infections has fallen by 19%.³ In 33 countries, the HIV incidence has fallen by over 25% from 2001 to 2009; 22 of these countries were in sub-Saharan Africa. In the Association of Southeast Asian Nations (ASEAN) region, the prevalence of HIV infection among Thai adult population (15 to 49 years) dropped from a high of 2.1% in 1995 to 1.3% in 2009, and in Cambodia, from 1.4% to 0.5% over the same period.⁴

A recent Cochrane review of behavioural interventions has showed that such interventions have been effective in HIV and sexually transmitted infection (STI) prevention, and have reduced the incidence and prevalence of HIV and STIs.⁵ A 2008 review of behavioural interventions to reduce sexual transmission of HIV among men who have sex with men (MSM) cited 44 studies evaluating interventions with 18,585 participants.⁶ Forty interventions were able to reduce unprotected anal sex by 27%; the other 18 interventions reduced unprotected anal sex by 17% beyond changes observed in standard or other interventions. Central to behavioural interventions has been advice on consistent and correct condom use. One of the few meta-analysis of the effectiveness of condoms in preventing HIV infection in 2002 estimated this to be 80%.⁷ A more recent evaluation of condom effectiveness has argued that studies of condom effectiveness are inherently complex and the potential forms of study bias all generally favour the null hypothesis.⁸

Antiretroviral Treatment (ART)

Scientific research and therapeutic trials led to the discovery and introduction of several anti-HIV medications from the late 1980s. An important milestone was reached in the mid 1990s when combinations (or cocktails) of antiretroviral (ARV) medications that included protease inhibitors were shown to be able to decrease viral replication, increase CD4+ lymphocyte count, halt or slow down immune suppression and improve prognosis in HIV-infected persons. Since then, programmes that have made combination treatment widely available in developed countries have been able to slow down clinical deterioration of HIV-infected persons, reduce opportunistic infections, cancers and other complications of HIV infection. Rapid advances in treatment and management have spread worldwide, massive aid programmes in developing countries are coordinated through organisations like the Global Fund for AIDS, Tuberculosis (TB) and Malaria, the Bill and Melinda Gates Foundation, The Elton John AIDS Foundation and the American Foundation of AIDS Research, just to name a few. Just as important as the scientific and medical advancements have been the role that AIDS activists and advocates have played in lobbying governments and politicians to take action to provide resources for the development of treatments and

care, and to change social, legal and structural barriers that stand in the way of AIDS prevention and control.

The combined effort of AIDS workers has led to dramatic increases in the delivery of treatment worldwide. UNAIDS estimates that 6.6 million people in low- and middle-income countries were receiving antiretroviral therapy (ART) in 2010, an increase of 1.4 million from a year earlier. However, it is also estimated that 9 million persons are waiting to receive ART, and for every person starting on ART, 2 people are newly infected. Based on current projections, a further 20 million people will be infected with HIV by 2031.⁹ It is clear that we cannot hope to control the pandemic unless and until we significantly improve prevention programmes.

Biomedical Strategies

Opportunities for biomedical prevention can be conceptualised according to stages before, during and after HIV infection. Male circumcision, vaccination, topical and oral pre-exposure prophylaxis (PrEP, giving ARVs to HIV-negative individuals to prevent acquisition of HIV) are possible strategies. In the immediate pre-coital, coital and immediate post-coital periods, intermittent topical and oral PrEP, as well as post-exposure prophylaxis (PEP) are possible. After the immediate post-infection phase is over, use of ART for infected individuals can prevent transmission, and this has now been named treatment as prevention (TasP).

However up till as recently as 2008, research into biomedical strategies had not been successful. A review article that year concluded that after disappointing findings in efficacy trials of vaginal microbicides, vaccines, the diaphragm and suppressive therapy for herpes, HIV prevention must continue to rely on condom promotion and other established strategies while biomedical approaches continue to be assessed and their implementation strategies evolve.¹⁰

Male Circumcision

A significant development was the results of 3 separate randomised controlled trials (RCTs) in sub-Saharan Africa released in 2007 that showed that adult male circumcision could reduce the risk of HIV acquisition in men (female-to-male transmission) by around 60%. Thirteen southern and eastern African countries with high HIV prevalence, low levels of male circumcision and generalised heterosexual epidemics are The World Health Organisation/The United Nations Joint Programme on HIV/AIDS (WHO/UNAIDS) priority countries for male circumcision scale-up and are moving forward at varying speeds to develop national programmes.¹¹ The role of male circumcision to prevent MSM or male-to-female transmission is as yet unproven.

Prophylactic HIV Vaccines

Disappointing results from clinical trials to develop prophylactic vaccines against HIV infection led many experts to believe that it may be unlikely that protective antibodies could be produced through vaccination. However the modest success of prime-boost combination RV144 vaccine trial in Thailand in 2007 has led to some degree of optimism.¹² Intention-to-treat (ITT) analysis involving 16,402 subjects showed a trend towards prevention of HIV-1 infection among the vaccine recipients, with a vaccine efficacy of 26.4% and in the per protocol analysis of 12,542 subjects, the vaccine efficacy was 26.2%. In the modified ITT analysis involving 16,395 subjects (with the exclusion of 7 subjects who were found to have had HIV-1 infection at baseline), the vaccine efficacy was 31.2%. Vaccine recipients developed a low level of gp120-binding antibodies and also developed a number of broadly neutralising antibodies (bNAbs) against HIV isolates, and this is a current focus of research into vaccine.

Pre-exposure Prophylaxis (PrEP)

Perhaps the most interesting biomedical interventions so far have been the use of ARV medications used to prevent HIV transmission. Proof of concept of PrEP has been demonstrated for some time by the success of ARV medications to prevent mother-to-child transmission (MTCT) of HIV. Providing ARV medications to pregnant mothers during labour and delivery and to newborn babies during breastfeeding significantly reduces the likelihood of infection. In 1994, the landmark ACTG 076 study showed zidovudine therapy reduced MTCT by 67%.¹³ Current evidence shows that when ART is initiated before 28 weeks' gestation and viral load is suppressed to <50 copies/mL near delivery, the use of combination ART is able to reduce the rate of transmission of HIV from approximately 20% to 30% to <0.5%.¹⁴

PrEP can be topically administered, in the form of microbicidal gels, vaginal rings, suppositories, capsules and films, or orally taken. Topical agents can achieve higher concentrations in genital tissues, have the potential for long-acting formulations, the potential of combination products, have little systemic toxicity, require less monitoring, and may be used during pregnancy and breastfeeding. Oral agents have the disadvantage of systemic exposure, potential for greater toxicity, requirement for monitoring, and there may be greater risk of viral resistance development, which may have an impact on the treatment regimens. Among ARV agents, the 2 most commonly trialed have been tenofovir (TDF, tenofovir disoproxil fumarate) and FTC/TDF (co-formulated emtricitabine + tenofovir). Both are potent with broad antiviral activity, have long half-lives compared with other ARV drugs, are able to block initial infection by acting

early in HIV life cycle, and FTC is rapidly active. They have favourable safety and tolerability, and are easy to take with low pill burden, no food restrictions and few drug interactions. However both TDF and FTC/TDF are used in first-line treatment regimens, and there are concerns about resistance as well as cross-resistance with drugs belonging to the same class of ARV agents.

In 2010, the first successful microbicide trial, Caprissa 004, reported that 2 doses of 1% TDF gel pre-coitally lowered the incidence of HIV infection by 39% among 889 women in South Africa. Those who had high adherence (>80% of sexual acts) had 54% reduction, compared to those who had low adherence (<50% of sexual acts, 28% reduction).¹⁵ These results could not however be confirmed in the larger Vaginal and Oral Interventions to Control the Epidemic (VOICE) trial involving 5029 women in South Africa, Zimbabwe and Uganda. The TDF gel arm of the study was stopped after routine review of study data concluded that the gel was not effective in preventing HIV infection in women enrolled in the trial.¹⁶

Also reported in 2010 was the iPrEX study that involved 2499 MSM in 11 sites in 6 countries taking daily oral FTC/TDF. Men randomised to the FTC/TDF arm were 44% less likely to become infected by HIV than those in the placebo arm, 64 infections in the placebo arm versus 34 in the treatment arm. Once again adherence was crucial; those who reported greater than 90% adherence had 68% efficacy, and those who reported less than 50% adherence had 16% efficacy.¹⁷ Researchers have examined drug levels in stored blood samples from participants who became infected and from those who did not. Participants who were infected were estimated to have taken less than 1 dose of ARV a week, those who remained uninfected had taken about 3 doses a week. It has been estimated that 4 doses a week of ARV reduced the risk of infection by around 96%. There are 2 RCTs on PrEP reported among heterosexuals. The Partners PrEP study on 4758 serodiscordant heterosexual couples in Kenya and Uganda in which seronegative partners were randomised to receive TDF, FTC/TDF or placebo, reported that those in the TDF and FTC/TDF arms were 67% and 75% less likely to become HIV-infected.¹⁸ A similar study on heterosexually active serodiscordant couples in Botswana, the TDF2 trial, showed that those in the FTC/TDF arm had reduced risk of HIV infection of 62.2%.¹⁹

However, the use of ART as prevention raises several concerns, including side effects and toxicity; development of drug resistance, especially when adherence to long-term use is an issue; risk compensation and whether and how much behaviour will change—whether PrEP will lead to reduced condom use and more sexual partners; finally and not least, is the issue of cost, access to ARV drugs, and who will pay for PrEP. Key implementation questions that need

to be answered are whom to target, and where to deliver the ARV e.g. STI clinics, HIV clinics, public health facilities, primary care clinics, or pharmacies. For public health impact, PrEP needs to achieve high access and coverage of highest risk persons. It is thought that there is now enough evidence to develop guidance for demonstration projects for the use of the oral FTC/TDF combination in certain populations like MSM and serodiscordant couples.

Post-exposure Prophylaxis (PEP)

PEP has been used for many years, even before the US Centers for Disease Control and Prevention (CDC) issued its recommendations in 2005.²⁰ Evidence from animal studies and human observational studies demonstrate that PEP administered within 48 hours to 72 hours and continued for 28 days might reduce the risk for acquiring HIV infection after mucosal and other non-occupational exposures. A 28-day course of ARV is given to persons who have had sexual exposure to blood or genital secretions of a person known to be HIV-infected or suspected to be at high-risk of having HIV infection, when that exposure represents a substantial risk for HIV transmission viz unprotected anal or vaginal intercourse. PEP should be initiated promptly for the best chance of success. Clinicians should perform a HIV test, relevant blood tests, provide a starter pack of 1 to 2 weeks and schedule a follow-up visit to review the results of baseline HIV testing (if rapid tests are not used), provide additional counselling and support, assess medication side effects and adherence, and provide additional medication if appropriate. Inherent clinical and ethical difficulties have made evaluation of PEP problematic. A systematic review was not able to draw conclusions on the clinical effectiveness of non-occupational PEP for HIV because of the limited evidence available; however the review suggested that PEP may be cost-effective, especially in certain population subgroups like MSM.²¹

Treatment as Prevention (TasP)

It is logical that the lower the amount of virus present in blood and genital secretions, the less likely that HIV transmission can occur. Serum viral load was found to be the chief predictor of the risk of heterosexual transmission of HIV in adults in the analysis of 415 initially serodiscordant couples in Uganda; there was also significant dose-response relation of increased transmission with increasing viral load.²² In a systematic review of HIV transmission, viral load and ART, the comparison of rates in patients on ART and not on ART indicate that heterosexual transmission was reduced by 92%, from 5.64 to 0.46 per 100 person-years.²³ Studies of heterosexual discordant couples observed no transmission in patients treated with ART and with viral

load below 400 copies/mL.

HPTN 052 was a large multicontinental RCT that evaluated the impact of immediate versus delayed therapy (not started until CD4 count <250 cells/mm³) in 1763 HIV serodiscordant couples.²⁴ The HIV-infected partner was ART naive and had a CD4 count of 350 to 550 cells/mm³. At entry, 98% of the participants were in heterosexual monogamous relationships, all received counselling on behavioural modification and condom use. Twenty-eight linked HIV transmission events were identified during the study period but only 1 event occurred in the early therapy arm. This 96% reduction in transmission associated with early ART was statistically significant (HR 0.04, 95% CI: 0.01 to 0.27, $P < 0.001$). These results show that early ART is more effective at preventing transmission of HIV than all other behavioural and biomedical prevention interventions studied to date, including condom use, male circumcision, vaginal microbicides, HIV vaccination, and pre-exposure prophylaxis. The HPTN 052 trial also found a reduction in extra-pulmonary TB in the patients who initiated ART early compared to those for whom treatment was initiated at later (3 vs 17 cases). Although this study was conducted among heterosexual couples, effectiveness of ART in preventing HIV transmission will likely apply to MSM and injecting drug users as well. At a WHO and U.S.NIH working group meeting in 2011, it was felt that there was reason to believe that early initiation of ART for HIV prevention will benefit MSM, transgender women, and others who have anal intercourse, although the magnitude of the effect may be different from that observed in heterosexual couples. It was felt that an additional individual randomised clinical trial in MSM was not warranted.²⁵

Even before these RCT results were available, evidence was accumulating that led some experts to propose increasing access to ART in order to prevent HIV transmission at the population level. In 2006, a group of WHO scientists produced a hypothetical modelling exercise to examine a strategy of universal voluntary HIV testing and immediate treatment with ART in the context of a generalised heterosexual epidemic. They showed that testing all adolescents and adults once a year, on average, and starting individuals on ART as soon as they test positive for HIV, would reduce the basic reproduction number (R_0) below 1 and eventually eliminate HIV.²⁶ The concept of a community viral load (CVL) emerged from the disproportionately high HIV infection level among black MSM in the US that was believed to be the result of a much higher overall viral load in that community when compared with other MSM communities, which in turn led to more efficient transmission of HIV and higher infection rates.²⁷ The relationship of CVL and the incidence of new HIV infections were reported in subsequent studies,²⁸ with

Table 1. Studies on Biomedical Strategies for HIV Prevention

Research Study	Caprissa 004	iPrEX	Partners PrEP	TDF2	HPTN 052	Male Circumcision	RV 144
Study Participants	Heterosexual women	MSM	Serodiscordant heterosexual couples	Serodiscordant heterosexual couples	Serodiscordant heterosexual couples	Heterosexual men	Heterosexual men and women
Type of Intervention	Coital TDF vaginal gel	Daily FTC/TDF pill	Daily TDF pill Daily FTC/TDF pill	Daily FTC/TDF pill	Early vs delayed ART treatment		ALVAC-HIV and AIDSVAX vaccine regimen
Reduced Risk of HIV (Overall)	39%	44%	62% (TDF) 73% (FTC/TDF)	63%	96%	54% (female to male transmission)	31%
Reduced Risk of HIV (Consistent Users)	54%	68%	-	78%	-	-	-

MSM: Men who have sex with men; TDF: tenofovir disoproxil fumarate; FTC: emtricitabine; ALVAC: recombinant canarypox vector vaccine; AIDSVAX: recombinant glycoprotein 120 subunit vaccine

one linking the drop in new infections to decreased CVL that was the result of increased use of ART.²⁹ There have been several analyses of the impact of early scaled up ART on the epidemic. In British Columbia, Canada, new HIV infections fell by about 50% between 1995 and 1998 after the introduction of ART, and have remained unchanged to the present despite a noticeable increase in syphilis rates.³⁰ In Taiwan, a study showed a 53% reduction in new positive HIV tests after the introduction of free access to ART; this reduction took place without any change in rates of syphilis.³¹ At that time there was still no evidence that early treatment of HIV could reduce transmission at the population level, and that evidence is now available.

On the strengths of observational, mathematical modelling and RCT data showing the positive impact of ART on disease progression as well as public health, the latest US Department of Health and Social Services (DHSS) guidelines has recommended ART for all persons with HIV infection, the strength of recommendation depending on the pre-treatment CD4 level.³² It has also recommended that ART be offered to all patients who are at risk of transmitting HIV to sexual partners. Thirteen countries and the regional guidelines for Europe are already recommending the use of ART to prevent HIV transmission for serodiscordant couples.³³

Mounting evidence for the efficacy of TasP has led to heightened interest and excitement among scientists, policy makers, programme managers and prevention specialists. There are currently more than 50 ongoing or planned field trials and analyses; these include a number of large RCTs. This enthusiasm has been tempered by concerns raised by community and patient groups calling for the need to ensure that human rights and ethics are at the centre of plans to scale up and roll out TasP programmes. These include ensuring that affected communities are involved

in programme planning, implementing and evaluation, addressing ethical and structural obstacles, making sure testing and treatment are voluntary and confidential, that all necessary information is provided before treatment is started, and that laws and policies should work towards an enabling and supportive environment for people with HIV AIDS (PWA).^{34,35} Furthermore, the critical roles of social scientists, education and communication experts in planning and implementation of biomedical prevention programmes cannot be overstated. Every biomedical intervention has behavioural and structural dimensions, for example, in order for PrEP to work, persons need to accept risk and vulnerability and take the medications as intended, and there must be changes to financial obstacles and new logistic arrangements introduced to deliver and maintain access to the ARV medications. Enthusiasm for TasP and PrEP will be tempered by the recognition that these programmes will be enormously expensive and may come at the expense of cutbacks in HIV programmes, the prospect of viral drug resistance and risk compensation. Table 1 summarises the findings of the major recent biomedical HIV prevention studies.

Singapore—Are We Ready for the Change?

The latest local statistics on HIV/AIDS reported that 461 residents were newly diagnosed with HIV infection in 2011; 449 acquired the infection through the sexual route, heterosexual transmission accounting for 46% of infections, and homosexual transmission 42% and bisexual transmission 9%.³⁶ In 2011, more than half (53%) of the new cases were in late-stage HIV infection (CD4+ cell count of less than 200 per cu mm or AIDS-defining opportunistic infections or both) when they were diagnosed; this was similar to the pattern in previous years. In 2011, for the first time in 20 years, there were more newly diagnosed

infections among MSM than among heterosexuals. Whilst much has been achieved to slow the spread of HIV infection in the last 30 years, particularly among sex workers, their clients and among MSM, the recent increase in infections among MSM in Singapore and the region has rung alarm bells.^{37,38} Several factors are thought to be contributing to this increase viz changing sexual mores, low condom use rates arising from safer sex fatigue and treatment optimism, HIV-related stigma, low levels of testing, low levels of disclosure, and late diagnosis. Other areas of concern are the use of recreational drugs and sex, use of the Internet for sexual liaisons, sex-on-premises venues, and the changing sex trade landscape. The high HIV incidence is unlikely to change soon, this is because existing HIV prevention strategies are only partially effective, a preventive vaccine remains elusive, and current therapies cannot cure HIV infection. We need to increase the range of prevention methods at our disposal. The use of ARV to prevent HIV transmission may be a turning point in our battle against the relentless spread of HIV.

The high proportion of infected persons presenting at the late stage of the disease means there is a very high CVL among communities at highest risk for HIV infection, in the local context this is undoubtedly MSM. While the percentage of HIV infection among Singaporean adults is in the order of 0.1%,³⁹ this author estimates the point prevalence of HIV infection among MSM in Singapore to be in excess of 5%. This is based on findings of the Action for AIDS's annual HIV testing projects conducted at the end of every year since 2007. These projects test over 1000 MSM each year, largely those who have not tested before or have tested negative before. In these projects, the rapid test positivity was 3.1%, 2.6%, 1.6%, and 2.8%, for the years 2007 through to 2010.⁴⁰ It is also based on the seropositivity of MSM clients at the Action for AIDS Anonymous Test Site which were 5.7%, 4.7%, 2.8%, 4.5%, and 5.4% for the years 2007 through to 2011.⁴¹ As mentioned above, male circumcision has not been shown to be effective in reducing HIV transmission among MSM, whereas PrEP is still problematic and somewhat farther down the road in terms of widescale roll out. Among MSM, it is the strategy of TasP, early diagnosis and early initiation of ARV treatment that will be likely be able to reduce the CVL. This approach is critically important to stop HIV transmission in the MSM community in Singapore. It could be introduced right now provided we have the commitment, funding and work towards an enabling environment.

An enabling environment will require the removal of structural, legal (specifically Section 377A of the Penal Code) and social barriers that stand in the way of education, and which entrench stigmatisation and discrimination of affected communities. This will allow greater mobilisation

and organisation of the MSM community, and lead to early and regular testing. Testing should be made easy and cheap. Those found to be HIV-infected must be linked to the treatment programmes. Treatment has to be made accessible and affordable and this requires an overhaul of current HIV treatment programmes and policies. HIV-infected persons should be provided a supportive and enabling environment that should include protection from dismissal from their jobs solely because of HIV infection.

The promising results from these new biomedical interventions have raised hopes for much more effective HIV prevention. It is clear that we cannot only rely on strategies based on traditional behavioural models of prevention if we are to stop the spread of HIV. Singapore's HIV programme must be increasingly based on evidence-based strategies, and science should be allowed to inform policy.

REFERENCES

1. Redefining AIDS in Asia - Crafting an Effective Response. Report of the Commission on AIDS in Asia. UNAIDS. Available at: http://data.unaids.org/pub/Report/2008/20080326_report_commission_aids_en.pdf. Accessed 1 June 2012.
2. Wong ML, Chan RKW, D Koh. The long term effects of condom promotion programmes for vaginal and oral sex on sexually transmitted infections among sex workers in Singapore, 1990-2002. *AIDS* 2004;18:1195-9.
3. UNAIDS Report on the Global AIDS Epidemic 2010. Available at: http://www.unaids.org/globalreport/documents/20101123_GlobalReport. Accessed 1 June 2012.
4. AIDS Data Hub. HIV prevalence and Epidemiological Status. Available at: <http://www.aidsdatahub.org/en/regional-profiles/key-affected-populations>. Accessed 1 June 2012.
5. Wariki WMV, Ota E, Mori R, Koyanagi A, Hori N, Shibuya K. Behavioral interventions to reduce the transmission of HIV infection among sex workers and their clients in low- and middle-income countries. *Cochrane Database Syst Rev* 2012;2:CD005272.
6. Johnson WD, Diaz RM, Flanders WD, Goodman M, Hill AN, Holtgrave D, et al. Behavioral interventions to reduce risk for sexual transmission of HIV among men who have sex with men. *Cochrane Database Syst Rev* 2008;3:CD001230.
7. Weller SC, Davis-Beatty K. Condom effectiveness in reducing heterosexual HIV transmission. *Cochrane Database of Syst Rev* 2002;1:CD003255.
8. Crosby R, Bounse S. Condom effectiveness: where are we now? *Sex Health* 2011;9:10-7.
9. UNAIDS. AIDS at 30 - Nations at the crossroads. Available at: <http://www.unaids.org/unaidresources/aidsat30/aids-at-30.pdf>. Accessed 1 June 2012.

10. Kaldor JM, Guy RJ, Wilson D. Efficacy trials of biomedical strategies to prevent HIV infection. *Curr Opin HIV AIDS* 2008;3:504-8.
11. Weiss HA, Dickson KE, Agot K, Hankins CA. Male circumcision for HIV prevention: current research and programmatic issues. *AIDS* 2010;24 Suppl4:S61-9.
12. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med* 2009;361:2209-20.
13. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med* 1994;331:1173-80.
14. Centers for Disease Control and Prevention (CDC). Achievements in public health. Reduction in perinatal transmission of HIV infection—United States, 1985-2005. *MMWR Morb Mortal Wkly Rep* 2006;55:592-7.
15. Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science* 2010;329:1168-74.
16. MTN statement on decision to discontinue use of tenofovir gel in VOICE. Available at: <http://www.mtnstopshiv.org/node/3909>. Accessed 1 June 2012.
17. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010;363:2587-99.
18. Baeten JM, Donnell D, Ndase P, Mugo NP, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012;367:399-410.
19. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med* 2012;367:423-34.
20. Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States. Division of HIV/AIDS Prevention, National Center for HIV, STD, and TB Prevention. Available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5402a1.htm>. Accessed 1 June 2012.
21. Bryant J, Baxter L, Hird S. Non-occupational postexposure prophylaxis for HIV: a systematic review. *Health Technol Assess* 2009;13:iii,ix-x.
22. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med* 2000;342:921-9.
23. Attia S, Egger M, Muller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. *AIDS* 2009;23:1397-404.
24. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011;365:493-505.
25. WHO and U.S. NIH Working Group Meeting on Treatment for HIV Prevention among MSM. Geneva, 26-27 October 2011. Available at: http://www.who.int/hiv/pub/msm_meeting_report.pdf. Accessed 1 June 2012.
26. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet* 2009;373:48-57.
27. Stall R. What's driving the U.S. epidemic in men who have sex with men? Presented February 4, 2008. http://www.retroconference.org/2008/data/files/retro2008_frameset.htm. Accessed 1 June 2011.
28. Das M, Chu PL, Santos GM, Scheer S, Vittinghoff E, McFarland W, et al. Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco. *PLoS ONE* 2010;5: e11068.
29. Montaner JS, Lima VD, Barrios R, Yip B, Wood E, Kerr T, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. *Lancet* 2010;376:532-39.
30. Montaner JS, Hogg R, Wood E, Kerr T, Tyndall M, Levy AR, et al. The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic. *Lancet* 2006;368:531-6.
31. Fang CT, Hsu HM, Twu SJ, Chen MY, Chang YY, Hwang JS, et al. Decreased HIV transmission after a policy of providing free access to highly active antiretroviral therapy in Taiwan. *J Infect Dis* 2004;190:879-85.
32. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at: <http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed 1 June 2012.
33. Antiretroviral Treatment as Prevention (TasP) of HIV and TB: 2012 update WHO/HIV/2012.12. Available at: http://whqlibdoc.who.int/hq/2012/WHO_HIV_2012.12_eng.pdf. Accessed 1 June 2012.
34. Treatment as prevention - Making it work for communities most affected by HIV. Campaign policy briefing (June 2012). International HIV/AIDS Alliance. Available at: <http://www.aidsalliance.org/includes/Publication/TAP-Policy-Briefing-2012.pdf>. Accessed 1 June 2012.
35. Articulating the global position of people living with HIV on ART for prevention. International Treatment as Prevention Workshop 2012. Available at: <http://www.treatmentaspreventionworkshop.org/wp-content/uploads/2012/05/P06.pdf>. Accessed 1 June 2012.
36. Ministry of Health Update on the HIV/AIDS situation in Singapore 2011. Available at: http://www.moh.gov.sg/content/moh_web/home/statistics/infectiousDiseasesStatistics/HIV_Stats.html. Accessed 1 June 2012.
37. Lim SH, Chan R. HIV infection among men who have sex with men in East and South-East Asia – time for action. *Sex Health* 2011;8:5-8.
38. van Griensven F, de Lind van Winjngaarden JW. A review of the epidemiology of HIV infection and prevention responses among MSM in Asia. *AIDS* 2010;24 Suppl 3:S30-40.
39. UNAIDS Country Estimates 2009. Available at: <http://www.unaids.org/en/regionscountries/countries/singapore/>. Accessed 1 June 2012.
40. Action for AIDS Community HIV Testing Project Statistics. Available at: http://afa.org.sg/Reports/MSMSP_2010_finalreport.pdf. Accessed 1 June 2012.
41. Action for AIDS Anonymous Test Site Statistics. Available at: http://www.afa.org.sg/Reports/ats/AfA_ATS_2011_Final.pdf. Accessed 1 June 2012.