Biomedical HIV Prevention Strategies: State of the Art and Implications for Public Health Policy in the Caribbean

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Recent advances in the field of biomedical prevention have induced optimism among both the scientific community and the public in general. The discussion of the research evidence is complemented with a discussion of the implications of this evidence for the Caribbean, highlighting the issues and controversies that should be considered in order to encourage and advance the responsible consideration of biomedical strategies. Traditionally, HIV prevention strategies have been characterized as predominantly behavior, social or biomedical. In practice, however, some strategies defy classification: even when they rely on technological or pharmaceutical elements, they have to be adopted by a society and the individuals within it. Moreover, whatever the strategy used, it will have to be distributed, implemented and made available through health care systems or other means. And its cost will be absorbed by specific funders or by society in general. Given the current historical context of the HIV/AIDS epidemic and the array of strategies required to control it, these distinctions (biomedical vs. behavior) can hinder the collaborations required to provide the needed combinations of strategies. The efficacy of the diverse strategies range from: 99% for programs to prevent MTCT, 63% for pre-exposure prophylaxis (PrEP), 96% for treatment as prevention, 39% for vaginal microbicides (54% with good adherence), post exposure prophylaxis (PEP), 31% for a vaccine and 53-60% for medical voluntary adult circumcision. To curtail and eliminate the HIV/AIDS epidemic in the future, expansion and scaled-up implementation of combinations of such strategies will be needed. [*P R Health Sci J 2012;3:170-179*]

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Thirty years after the onset of the epidemic, HIV/AIDS continues to affect most-at-risk populations. There is still much to do to control the epidemic, using multiple approaches to deal not only with different risk factors but also with different populations. HIV/AIDS is not just a disease or a pathogen; it is an illness that has expanded because of social and economic disparities. Recent advances in the field of biomedical prevention have stirred optimism among both the scientific community and the general public since the approval by the FDA of a combination drug for the prevention of HIV sexual transmission. While acknowledging the theoretical efficacy of behavior interventions, practitioners and researchers also recognize that these have had limited success due to diverse factors, including the need for sustained resources and infrastructure.

This review summarizes the diverse strategies studied and/or proposed as biomedical prevention interventions. It will not include behavior interventions, although we recognize that these are essential elements in prevention as well as important adjuncts to the success of the biomedical strategies. Examination of this evidence can shed light on the need to adopt some of the strategies to address HIV transmission in high-risks areas and within targeted high-risk populations. The discussion of the research evidence and its implications for the Caribbean will highlight the issues and controversies that need to be taken into account in encouraging responsible consideration of biomedical strategies.

HIV and AIDS: The burden of the disease

We are still witnessing large numbers of new infections in addition to increased number of survivors undergoing treatment. These two trends result in a high burden of disease, which in turn creates a rising need for services: prevention, care, education, and workforce resources. A recent UNAIDS report

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estimates that, at the end of 2010, approximately 34 million people (31.6 to 35.2 million) were living with HIV worldwide, up 17% from 2001. These estimates reflect both new cases and the increased survival and reduction of AIDS-related deaths due to access to antiretroviral therapy (1). Worldwide, there were 2.7 million (2.4 -2.9 million) new HIV infections in 2010, including an estimated 390,000 (340,000-450,000) among children. This was 15% less than in 2001, and 21% less than the number of new infections at the peak of the epidemic in 1997 (1). Increases in antiretroviral therapy (ART) coverage have occurred in sub-Saharan Africa as a result of greater funding and expansion of treatment programs, which experienced a 20% increase between 2009 and 2010 alone. An estimated 6.6 million people in low- and middle-income countries are receiving HIV treatment. This is an increase of more than 1.35 million over the previous year. In low- and middle-income countries, 47% of the 14.2 million eligible people living with HIV were on ART at the end of 2010, compared to 39% at the end of 2009.

The prevention of mother-to-child-transmission (MTCT) has been particularly successful. Expanded prenatal HIV counseling and testing programs have facilitated the treatment of women during pregnancy with diverse antiviral regimens. Over the past two decades, researchers have shared epidemiologic data on observational, retrospective, small and large randomized clinical trials of behavior, biomedical and combined strategies to control the epidemic. Approaches have included an emphasis on counseling and testing of at-risk populations including pregnant women, antiviral medications to reduce the risk of MTCT, treatment of people living with HIV presenting at different stages of disease, treatment of sexually transmitted infections and treatment of at-risk populations. The HIV/AIDS epidemic has highlighted the limitations in the health infrastructure, the adverse impact of social and perceived stigma, the constraints in health education and community involvement, and, in some countries, the lack of political will to provide the necessary resources to improve the health status of current and future generations. One harsh reality is that the need for treatment will continue to rise unless the epidemic is controlled; current budgets will not suffice to cover prevention and treatment needs worldwide.

The Caribbean epidemic

Although the Caribbean accounts for a relatively small share of the global epidemic, HIV prevalence among adults in this region is about 1.0%, which is higher than in all other regions outside sub-Saharan Africa. Unprotected sex is the primary mode of transmission in the region.

There has been significant progress within the Caribbean region. New HIV infections have been reduced by a third from 2001 levels; HIV incidence has decreased by 25% in the Dominican Republic and Jamaica and by 12% in Haiti. Increased access to HIV prevention services for pregnant women has decreased the number of children newly infected with HIV and AIDS-related deaths among children. Increased access to antiretroviral therapy has led to a considerable drop in mortality associated with AIDS (2).

Because the Caribbean epidemic is strongly associated with heterosexual contact and commercial sex, there are specific populations that could receive the benefit of intensive behavior and biomedical prevention interventions. The HIV prevalence is highest among men who have sex with men (MSM) and among sex workers in the Caribbean. From 2006-2008, the prevalence of HIV among sex workers varied from 2.7% in the Dominican Republic to 27% in Guyana. This population serves as a bridge for transmission; for example, in Jamaica 25% of reported cases of AIDS indicated unprotected sex with female sex workers as mode of acquisition. The HIV prevalence among MSM varied from 6.1% in the Dominican Republic to 32% in Jamaica (3).

During the past 8 years, donors provided over US$1.3 billion to support the regional and country responses to HIV. The antiretroviral treatment (ART) coverage rose from 1% in 2004 to 51% in 2008, resulting in a 40% reduction in the number of AIDS-related deaths in that year. In the area of pediatric AIDS treatment, the coverage has reached 55%; this has contributed to the reduction of AIDS-related mortality. Progress has also been made in voluntary counseling and testing over the past 5 years. In 11 Caribbean countries, more than 90% of pregnant women are tested for HIV every year. In Haiti, 1,000,000 people were tested for HIV between 2008 and 2009; among these were approximately 300,000 pregnant women. Prevention of mother-to-child transmission (MTCT) coverage is 52%. This has reduced the number of new infections among children by 18% (3).

Biomedical prevention interventions and strategies: What does the evidence say?

HIV prevention refers to practices or strategies used to prevent the spread of HIV. These include individual practices, as well as large-scale strategies instituted by governments or other organizations as public health policies. Biomedical prevention interventions are defined as those that require individuals to use devices or drugs. They contrast with behavior interventions, which rely on personal changes to achieve the same purpose. Examples of the latter include sex education; needle-exchange programs; safe injection sites; safe sex; sero-sorting; sexual abstinence and immigration regulation. In practice, however, some strategies defy classification: even when they rely on technological or pharmaceutical elements, they have to be adopted by a society and the individuals within it. Moreover, whatever the strategy used, it will have to be distributed, implemented and made available through health care systems or other means. And its cost will be absorbed by specific funders or by society in general. Given the current historical context of the HIV/AIDS epidemic and the array of strategies required to control it, these distinctions (biomedical vs. behavior) can hinder the collaborations required to provide the needed combinations of strategies.

This review will cover the following biomedical strategies: prevention of mother-to-infant transmission (MTCT), pre-exposure prophylaxis (PrEP), treatment as prevention (TASP), vaginal microbicides, post exposure prophylaxis (PEP), vaccines and circumcision. We emphasize, however, that although the biomedical element is at the core of each strategy, all of them will require behavior, social, economic, political and cultural adaptations for eventual success. The efficacy of most of these strategies has been proved in randomized clinical studies, as summarized in Table 1 and Figure 1.

Prevention of mother-to-child transmission (MTCT)

The best example of the efficacy of biomedical interventions is the prevention of mother-to-child transmission (MTCT). The Pediatric AIDS Clinical Trials Group 076 (PACTG 076) demonstrated that the administration of zidovudine (ZDV) to a pregnant woman and her infant could reduce the risk of perinatal transmission by nearly 70% (4). This strategy had the following impacts: blocking maternal HIV replication and reduction in maternal viral load; providing fetal prophylaxis by having drugs that "cross the placenta" and provide potential blocking of an infection in the fetal compartment; providing neonatal treatment to limit potential infection or viral replication in a post-exposure prophylaxis. Treatment during pregnancy, labor and delivery and neonatally to the infant is the standard of care in developed countries. Modifications to the original regimen led to other cost-effective strategies. Today MTCT rates are under 2% in most places where antenatal testing and treatments are available.

Two additional strategies have had an impact on the MTCT: elective cesarean section as the mode of delivery, and the use of infant formula. A randomized clinical trial demonstrated that 1.8% of infants born to women randomized to undergo cesarean delivery were HIV infected, compared with 10.5% of infants born to women randomized to vaginal delivery (P <0.001) (5). Results from a large meta-analysis of individual patient data from 15 prospective cohort studies also demonstrated the benefit of scheduled cesarean delivery, with a 50% reduction in risk (6).

In surveillance data from the United Kingdom and Ireland, pregnant women receiving combination ARV regimens (at least 3 drugs) had transmission rates of about 1%, unadjusted for mode of delivery. The transmission rate among all women who received at least 14 days of ARV medications was 40 (0.8%) of 4,864, regardless of mode of delivery. It seems that the additional benefit of the elective cesarean section is lost in the presence of potent combination ART (7).

In the United States, where safe infant feeding alternatives are available and free for women in need, HIV-infected women should not breastfeed their infants. In international settings nevirapine (NVP) alone or combined with ZDV can reduce the risk of postnatal infection during breastfeeding (8). Other studies have evaluated the use of prolonged maternal ART to reduce transmission during the breastfeeding period up to six months in Sub-Saharan Africa (9, 10). These strategies --combination ART during pregnancy, labor, post-partum to the mother or the infant; elective cesarean section; and/or the use of infant formula-- have been proven effective in reducing the MTCT at different points in the perinatal period. By far the most potent and effective strategy is ART during pregnancy. Unfortunately, not all women benefit from antenatal testing and early therapy because of lack of access to services.

In the Caribbean, MTCT constitutes an estimated 8-10 percent of all HIV, with an estimated HIV prevalence among pregnant women of 1.1%. Programs for the prevention of MTCT have been widely implemented in the region. The estimated percentage of pregnant women with HIV in the Caribbean who received ARV for MTCT increased from 29 percent in 2007 to 52 percent in 2008. Nevertheless, successful prevention has been geographically uneven. Reported mother-to-child transmission rates of HIV by country ranged from 0 percent to 28, highlighting significant disparities in the region. The reported ART coverage of HIV positive pregnant women is similarly varied, ranging from 100 percent of women tested in some countries, to less than 50 percent in others (11, 12, 13).

Pre-exposure prophylaxis (PrEP)

PrEP refers to treatment with antivirals prior to the exposure to HIV. Again, part of the scientific rationale comes from the experience in MTCT. The results of a study called iPrEx provided the first evidence that oral PrEP can help prevent HIV. A combination of two drugs: emtricitabine (FTC) and tenofovir (TDF) was studied in Peru, Ecuador, South Africa, Brazil, Thailand, and the United States. The drug was taken daily and the intervention included a comprehensive HIV prevention package (risk-reduction counseling, condoms, regular HIV testing). A 44% reduction in HIV acquisition was reported. The efficacy was strongly associated with detection of the drug in the blood, which is a direct marker of adherence. In the FTC/TDF group, the study drug was detected in 22 of 43 of sero-negative subjects (51%) and in 3 of 34 HIV-infected subjects (9%) (P<0.001) (14).

In contrast, a trial of the same drug as the iPrEx (TDF/FTC) offered to high-risk women was discontinued because an equal number of infections occurred in both the placebo and treatment groups (FEM-PrEP) (15). The study had enrolled 2,119 higher-risk women between the ages of 18 to 35 in Kenya, South Africa and Tanzania. High-risk women were defined as those with frequent sexual intercourse or who had more than one sex partner. Further analysis showed that the women in the trial did not show adequate adherence to the daily PrEP regimen. A recent analysis of the use of contraceptives among the FEM-PrEP participants suggests that the adherence to the TDF could have been compromised by the contraceptive requirement for

the study. The researchers suggest that the adherence to both oral medications, contraceptive pill and TDF, was affected among those who were not using hormonal contraception prior to the study. This association is important to study further because the interaction between the oral contraceptive and the TDF was initially proposed as the mechanism for failure, suggesting that the study drug levels were decreased in the presence of hormonal contraception.

The fact that some studies show efficacy in both genders while others (FEM PrEP) show a lack of efficacy, has challenged the scientific community and dampened the optimism for the future use of the interventions. It is clear that good adherence is essential to the success and efficacy of PrEP to the same degree that it is important with treatment (16).

A study sponsored by the CDC (TDF2 Trial) in Botswana also found that daily oral TDF/FTC reduced risk of HIV infection in female and male participants. The TDF2 Study recruited 1,200 heterosexual men and women in Botswana and reported 62.6% fewer infections in the TDF arm compared with the placebo group (17). The efficacy of TDF/FTC in men was 80%, with two HIV infections in men on TDF/FTC versus ten on placebo, and this was statistically significant. The efficacy in women was 49%, with seven infections on TDF/FTC vs.14 on placebo, and was not statistically significant (17).

The safety and effectiveness of daily use of two antivirals (TDF or TDF/FTC) among heterosexual men and women in committed relations with partners who are HIV+ was carried out in Uganda and Kenya (Partners PrEP Study). The study enrolled 4,758 sero-discordant couples. When compared with placebo, those who took TDF had 62% fewer HIV infections and 73% fewer infections among those who took TDF/FTC as a combined tablet. The trial found very high rates of adherence and high rates of protection for both TDF and TDF/FTC for both HIV- negative women and men. Through May 31, 2011, a total of 78 HIV infections occurred in the study: 18 among those assigned TDF, 13 among those assigned to FTC/TDF, and 47 among those assigned placebo. Thus, those who received TDF had an average of 62% fewer HIV infections (95% CI 34 to 78%, p=0.0003) and those who received TDF/FTC had 73% fewer HIV infections (95% CI 49 to 85%, p<0.0001) than those who received placebo (18).

The reasons for the difference between the results of the IPrEx (carried out among MSM), the TDF2 female cohort and the FEM-PrEP are not clear. It has been suggested that the oral doses of TDF are insufficient to produce the necessary concentrations in the female genital tract to prevent HIV acquisition (19, 20).

The FDA used this data to support the recent approval of FTC/TDF for PrEP. In August, 2012 The CDC published an interim guidance regarding PrEP with TDF/FTC. It should be used for high risk heterosexual men and women and among discordant HIV couples during attempts to conceive. PrEP is contraindicated among persons of unknown or positive HIV status. Women of reproductive age should have a pregnancy test before beginning PrEP, http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6003a1.htm?s_cid=mm6003a1_w.

Treatment as prevention (TASP)

The concept of treatment as prevention follows the scientific model of MTCT. Since the plasma HIV-1 RNA concentration is now considered one of the key factors for HIV transmission, the use of Highly Active Antiretroviral Therapy (HAART) can be very effective in reducing the plasma HIV-1 RNA to undetectable levels, and consequently decreasing the risk of transmission to others (21). This reduction in risk has been demonstrated in MTCT, among sero-discordant heterosexual couples, and among injection drug users. Five observational reports noted substantial reduction of HIV transmission to a sexual partner when the HIV-infected index case was given ART (22). Lower community viral load resulting from the expansion of HAART coverage has been associated with declining numbers of new HIV diagnoses in Taiwan, British Columbia, Canada, and San Francisco, USA. As expressed in an editorial by J. Montaner, "The evidence is clear: treatment conclusively prevents morbidity, mortality, and transmission" (23).

People living with HIV who are receiving therapy have not only registered personal gains related to controlling the viral replication, but also improved their immune system, decreasing the chances of opportunistic infections, and decreasing mortality risks. Equally significant, this strategy reduces the risk of transmission to partners. At the same time, there is some concern that reducing the lethality and transmissibility of HIV has lessened fear of the disease and therefore lowered the guard among some populations. However, sexual disinhibition and an increase in risk practices may occur as a consequence of the perception that people are not infectious. In addition, treatment can have side effects and complications.

Considering that people with HIV will benefit from treatment, and that treatment may reduce their viral load sufficiently to reduce transmission risk to others, then treatment can be considered a preventive strategy. The HPTN 052 study was a randomized controlled trial that studied the efficacy of ART in the reduction or interruption of HIV transmission from an index patient with HIV to his or her sexual partner (24). The results from this trial were so dramatic that Science chose the study as its "Breakthrough of the Year" for 2011. The findings from the study showed a 96% reduction of HIV transmission attributed to the use of antiretroviral drugs (25). The cost estimate of worldwide implementation of providing ART to people living with HIV to replicate the outcomes from the HPTN 052 is around 35 billion dollars (26).

One ethical issue that emerges from this evidence is whether making people less infectious justifies initiating treatment

regardless of immune status. The salient question is: what value should be given to the personal benefit of an individual who will need therapy at some point vs. the societal benefit of having this person under antiviral therapy early? Could we reach a point where people would be coerced to receive treatment or face isolation? Examples of these strategies include the management of people with active tuberculosis in certain settings. Directly-observed therapy (DOT) in which a health care professional a health care professional or service provider administers the medication at a clinic, home or institution is currently used to treat tuberculosis, provide methadone and even HIV therapy. Would people with HIV be subjected to DOT or some coerced treatments? How about the concerns with side effects or complications?

Vaginal microbicides

Microbicides are substances that would reduce the spread of HIV and other sexually-transmitted diseases (STDs) and could be developed in different preparations, including gels, creams, suppositories, films, lubricants, sponges, or vaginal rings. They could be used in the vagina or rectum. Proposed mechanisms of action would include: killing or inactivating the virus or pathogen; altering the vaginal pH to increase the protective barrier; creating a coating to block viral entry into cells; blocking access to cells or limiting viral replication. Having a method that does not need negotiation or partners' consent would be of great preventive impact, particularly for women. Because these are substances that need to be inserted in the vagina or rectum, they would have to meet particular requirements; issues such as taste, odor, tolerance to heat and moisture would have to be taken into account, together with efficacy with short-term or long term use, pregnancy protection or lack of, protection from other sexually transmitted infections, cost and overall client acceptance.

The Center for the AIDS Program of Research in South Africa (CAPRISA) 004 trial assessed the effectiveness and safety of a 1% vaginal gel formulation of TDF for the prevention of HIV in women. This double-blind, randomized controlled trial was conducted comparing TDF gel (n = 445 women) with placebo gel (n = 444 women) in sexually active, HIV-uninfected 18- to 40-year-old women in urban and rural KwaZulu-Natal, South Africa. The TDF gel reduced HIV acquisition by an estimated 39% overall, and by 54% in women with high gel adherence (>80%). HIV acquisition was inversely correlated with detection of TDF in the vaginal secretions, probably related to product adherence (27).

In a May 2010 report, *A Community-led Advocacy Agenda for Microbicides*, ICASO documented the Jamaica AIDS Support for Life (JASL) involvement in microbicide advocacy in the Caribbean. JASL reports five goals and "lessons learned" from its microbicide advocacy work. These, which could serve as guidelines for other Caribbean communities preparing for the advent of microbicides, are as follows: 1) Involve individuals from a wide variety of professions and backgrounds to give the microbicide working groups legitimacy and increase their effectiveness, 2) educate in HIV science and prevention research bioethics, 3) offer advocates user-friendly tools and training in communications and public presentation to empower them in their role of developing public awareness, 4) integrate rectal microbicides into all microbicides advocacy work in order to strengthen consensus for the cause, and 5) get women excited about the potential of microbicides as a vital component of movement building (28).

Post-exposure prophylaxis (PEP)

Although medical treatment following HIV exposure (be this sexual, injection-drug related or other non-occupational) is less effective than preventing HIV infection by avoiding exposure altogether, several protocols recommend treatment for such incidents. PEP is short-term antiretroviral treatment to reduce the likelihood of HIV infection after occupational or sexual exposure. The mechanism of action is believed to be similar to the proposed for the prevention of MTCT, in which the exposed infants are treated with antiviral drugs for a period of 2-6 weeks post-natally. Although policies support the treatment of occupational exposure in the USA and other countries, there is debate on the need to use PEP after sexual exposure.

Vaccines

An effective and safe preventive vaccine has been and continues to be the aspiration of many scientists and clinicians worldwide. The STEP Study directly assessed the efficacy of a cell-mediated immunity vaccine to protect against HIV-1 infection or change in early plasma HIV-1 levels. This vaccine did not prevent or reduce early viral level. An exploratory analysis found higher risk of HIV infection (hazard ratio) among men who received the vaccine and were seropositive for Ad5 and for men who were not circumcised compared with placebo. The increased risk was not seen among circumcised men or those without titers to Ad5 (29, 30). The results of the STEP study raised important questions in the field of HIV vaccines, including the use of recombinant adenovirus vectors as immunogens, the need for the development of T-cell-based vaccines, the assessment of immunogenicity and the challenge models used. This in turn led to a new trial (RV 144 in Thailand) to test a canarypox vector vaccine (ALVAC-HIV) boosted with a recombinant glycoprotein vaccine (AIDSVAX B/E). This regimen provided a 31% protection against HIV-1 infection to the participants from low-risk populations at the end of 3.5 years (29, 30).

The search for an effective vaccine continues. This strategy is particularly appealing because its efficacy would be independent of adherence, giving it a significant advantage. The major challenge lies in developing a vaccine that is highly effective as well as safe. Safety is an important element for the ultimate

approval of a vaccine because it would be injected into millions of healthy individuals worldwide. Another hurdle lies in correcting misperceptions about vaccines. Many individuals think that the vaccine would include the live virus and would therefore cause infection. The use of live virus vectors such as with polio vaccines has not been endorsed by the scientific community.

Adult male medical circumcision (AMMC)

A large number of observational studies in Africa and in the United States have demonstrated that male circumcision reduces the risk of HIV infection in men. Three randomized trials in Africa have demonstrated that AMMC decreases HIV acquisition in men by 51% to 60%, and the long-term follow-up of these study participants has shown that the protective efficacy increases with time from surgery. Whether this protective effect extends to MSM is not clear. There may be protection with insertive practices but not with receptive anal intercourse.

Male circumcision has been shown to decrease the risk of acquiring genital herpes by 28% to 34% and the risk of developing genital ulcers by 47% in two trials. These trials also found that male circumcision reduced the risk of oncogenic high-risk human papillomavirus (HR-HPV) by 32% to 35% (31, 32, 33). Although the principal benefit of adult male medical circumcision is for the males, one trial reported benefits for the female partners of circumcised men by decreasing their risk for several sexually-transmitted infections. The risk of bacterial vaginosis was reduced by 40%, high-risk human papilloma virus was reduced by 28%, and trichomoniasis was reduced by 48% among the female partners of men with AMMC (31, 34). Although the benefit to women is clear if their male partner does not acquire HIV, we don't know if there would be benefits to the female partners of men who are already HIV infected.

One randomized controlled trial suggested no immediate benefit of AMMC in the reduction of transmission from infected men to their female partners (35), but an older observational study and a recent prospective study showed reductions of up to 46% in male-to-female transmission (36, 37). The potential population-level beneficial effect of adult medical male circumcisions has been estimated to reduce infections for both men and women up to 28% in Zimbabwe (38).

After using mathematical models and cost-effectiveness analyses, the Joint United Nations Program on HIV/AIDS (UNAIDS) and the World Health Organization adopted a policy advocating voluntary adult male circumcision in countries and regions with heterosexual HIV epidemics (39).

Neonatal circumcision

Neonatal circumcision was the standard practice for many years in many countries, including the USA. But this practice decreased in the USA following changes in the guidelines of the American Academy of Pediatrics and other entities. The HIV/AIDS epidemic has prompted a re-evaluation of the potential benefits and impact of incorporating the practice and making it available to parents with proper information and guidance. Technological advances in the technique and the administration of local anesthetic products should lower the risk and discomfort with the procedure. One advantage of neonatal procedures over adult circumcision is related to the fact that sex before the wound has healed was associated with a transient increased risk of HIV acquisition in men and this would not be observed in neonates (33).

A cost-effectiveness analysis on neonatal male circumcision in the United States published by the CDC projected an increase in quality-adjusted life-years and cost savings due to reduced HIV infections and their treatment costs. When other benefits of the intervention (i.e., protection from genital herpes, bacterial vaginosis, trichomoniasis, penile cancer and cervical cancer) were included in the analyses, the economic benefits were further enhanced. Despite its potential benefits, neonatal circumcision has many opponents. These argue that the procedure constitutes genital mutilation done without the infant's assent and only with parental consent. They suggest that the procedure be delayed until 18 years of age, when the man can provide informed consent. Nevertheless, parents routinely provide consent for preventive procedures such as immunizations, and for circumcisions done for religious reasons (40-41).

In the Caribbean, health professionals and advocates are divided on the benefits of adopting and even promoting circumcision as a preventive option at the individual and collective levels. The controversy is rooted in the social, economic and cultural characteristics of the HIV epidemic in the region. Some argue that introducing circumcision might jeopardize negotiation over condom use, especially given the dynamics and unequal power within sexual partnerships of girls, women, and men who have sex with men. Circumcision, it is feared, may become a 'badge' and a source of stigmatization. Moreover, the practice would require altering social norms regarding virility, sexual performance, and male identity which are difficult to change. Affordability and questions concerning the safety of the procedure are also potential barriers to adopting circumcision for HIV prevention.

What lies ahead

We have reached a point in the HIV/AIDS epidemic in which we can imagine a world without AIDS. This is theoretically possible, as has been shown with mathematical modeling which simulates how the epidemic has evolved and how it may be contained. In a paradigm-changing analysis, in 2009 Granich and associates ignited a debate regarding a strategy now known as "test and treat". Using data from South Africa, they modeled a strategy for universal voluntary testing and immediate treatment with ART. According to the authors this strategy "could reduce HIV incidence and mortality to less than one case per 1000

people per year by 2016 within 10 years of full implementation of the strategy and reduce the prevalence of HIV to less than 1% within 50 years." They estimated that in 2032, the yearly cost of the strategy would be US$1.7 billion (42).

Implementing such a strategy for universal HIV testing and immediate ART in the United States (or in many regions, including the Caribbean) would present many challenges that would have to be addressed. These include the large number of people who do not know their HIV sero-status, the limited access or delay in access to care of vulnerable populations, the prevalence of social and perceived stigma, difficulties with adherence to medication regimens, the presence of co-morbidities among the most vulnerable populations (e.g., mental health issues and substance use) and the well-known social determinants of health such as poverty, limited education, legal marginalization, and gender and power issues, to mention a few. The cost involved in expanding the health care system, training health care providers and providing universal testing, care and medications is another major challenge.

Addressing the question of the feasibility of eliminating HIV in the USA, David Holtgrove used an epidemiologic transmission model to demonstrate that if the HIV transmission rate were reduced by 50%, then the reproductive rate of HIV infection would drop below unity and lead to eventual elimination of infection. Attaining this goal would require allocating and expanding resources beyond the current levels (43).

Another tantalizing possibility is suggested by the case of a single patient who appears to have successfully fought off the disease. The "Berlin Patient", a man living with HIV who underwent a transplant involving HIV-resistant stem cells in

Table 1. Randomized studies for biomedical HIV prevention strategies: Main features and results efficacy

Strategy	Study name	Countries	Population	N	Study agent	Time frame	Efficacy
MTCT	UK & Ireland trial[7]	United Kingdom and Ireland	Singleton infants	5,930	HAART	18 months of age	99%
Pre-Exposure Prophylaxis (PrEP)	Partners PrEP[45]	Kenya & Uganda	HIV serodiscordant couples	4,758	Oral FTC/TDF and Oral TDF	24 to 36 months	63% for TDF
	TDF2/CDC 4940[45]	Botswana	Heterosexual men and women	1,200	Oral FTC/TDF	12 months	62%
	IPrEx[14,45]	Brazil, Ecuador, Peru, South Africa, Thailand and USA	MSM and transgender women	2,499	Oral FTC/TDF	36 to 42 months	44% (73% with good adherence)
	FEM-PrEP[15]	Kenya, South Africa and Tanzania	High risk women	1,950	Oral FTC/TDF	10 to 38 months	Study discontinued; lack of efficacy
	Voice/MTN033[45]	South Africa, Uganda & Zimbabwe	Women	5,021	Oral FTC/TDF, Oral TDF & vaginal tenofovir gel	14 to 36 months	Oral TDF stopped for lack of efficacy (data has not been released)
ARV treatment for prevention	HPTN 052[24]	Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand and Zimbabwe	HIV serodiscordant couples	1,763	Early initiation of ART	60 months	96%
Microbicide	Caprisa 004[45]	South Africa	Women	889	Vaginal tenofovir gel	30 months	39% (54% with ood dherence)
HIV Vaccine	RV 144[29]	Thailand	Heterosexual risk	16,402	Prime boost combination of two vaccines: AIVAC (the prime) and AIDSVAX B/E(the boost)	36 months	31.2% at 42 months (52% at 24 months)
	STEP Study/ HVTN 502[46]	North America, South America, Caribbean, Australia	Seronegative participants	3,000	MRKAd5 HIV-1 gag/pol/nef vaccine	210 to 338 weeks	Neither prevented infection nor lowered viral setpoint
Male circumcision	South African trial[47]	South Africa	HIV negative men	3,128	Medical male circumcision	21 months	60%
	Ugandan trial[48]	Uganda	HIV negative men	4,996	Medical male circumcision	24 months	57%
	Kenyan trial[49]	Kenya	HIV negative men	2,784	Medical male circumcision	24 months	53%

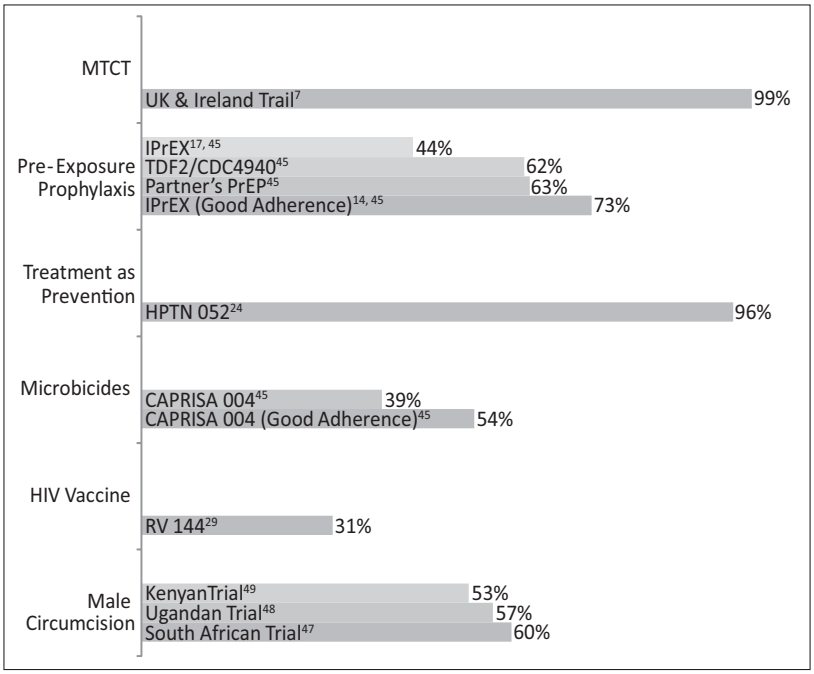

Figure 1. Randomized studies for biomedical HIV prevention strategies: Summary of results efficacy

2007 for the treatment of leukemia, was classified as cured of his HIV. Following the transplant, the man remained off the anti-HIV treatment for more than three years with normal CD4 counts and no evidence of HIV replication (44).

As we have described, the efficacy of the diverse biomedical strategies ranges from 99% for programs to prevent MTCT, 63% for PrEP, 96% for treatment as prevention, 39% for vaginal microbicides (54% with good adherence), 31% for a vaccine and 53-60% for medical voluntary adult circumcision (see table 1 and figure 1). It is important to emphasize that, so far, with the exception of a vaccine (once dosing is completed) and with circumcision (once healed), all of the proposed biomedical interventions require patient education and consistent adherence. To curtail and eliminate the HIV/AIDS epidemic in the future, expansion and scale-up implementation of combinations of such strategies will be needed.

Critical steps for the Caribbean: From evidence to action

As new evidence concerning efficacy emerges, new challenges arise concerning efficiency and cost-effectiveness, safety, acceptability, and ethics. At the forefront of these advances, the Caribbean faces a renewed opportunity to address HIV/AIDS using a regional framework. This regional framework could pool resources and monitor the use of preventive options, insuring that these are integrated into the national plans, targets, and budgets currently pursued by the countries in the region.

The Caribbean has been recognized for having carried out significant studies establishing mechanisms for collaboration in fighting HIV/AIDS across the different countries. These collaborative responses have been spearheaded by organizations such as the Pan Caribbean Partnership, the Coalition of National Programme Coordinators, Trans Caribbean HIV/AIDS Research Initiative and the Caribbean Regional Network of People Living with HIV. Despite these cooperative efforts, the HIV epidemic has had a differential impact on some countries within the region. Such intra-regional disparities inevitably mean that the individual countries assign different priorities to fighting HIV in their budgets. The contrasting realities of a track record in cooperative efforts and differing budgetary capabilities suggest the need for adopting a regional framework to consider biomedical prevention strategies on a larger scale and among varied populations.

Mounting evidence suggests that the successful adoption of biomedical approaches require combining these with behavioral and social approaches. Given the promise of new interventions, a profound evaluation of past successes and failures and of current strategies to address HIV in the regional should be a regional priority. The region can benefit from identifying experiences and knowledge emerging at the local level.

Moving forward, the region needs to recognize the desirability of strengthening testing and treatment, reducing stigmatization and gender inequality, and increasing levels of adherence. These continue to be preconditions for the incorporation of biomedical prevention strategies into national agendas. The leading regional networks and coalitions should take the lead in developing a set of guidelines for the adoption and adaptation of emerging prevention interventions. In keeping with the principles provided by PAHO for MCTC initiatives, these guidelines should be based on the following values and practices: universal access, client-centered services, the centrality of prevention and primary care, country-driven, regional collaboration, enhanced community involvement, intercultural perspective, and respect for human rights and gender parity (50).

Resumen

Avances recientes en el área de prevención biomédica del VIH han generado optimismo entre la comunidad científica y el público en general. Resumimos los hallazgos de diversos ensayos clínicos que han demostrado la eficacia de estrategias

categorizadas como biomédicas, a la vez que señalamos las implicaciones y controversias que éstas podrían suscitar en la región del Caribe. Aunque tradicionalmente las estrategias preventivas se han clasificado como biomédicas, de conducta, o sociales, muchas modalidades desafían esta categorización: aún los tratamientos basados en fármacos requieren cambios de conducta de parte del paciente y el apoyo de su entorno social. La eficacia de las estrategias discutidas en este artículo varían significativamente: 99% para los programas de reducción de transmisión de madre a infante; 63% para profilaxis pre-exposición (PrEP-siglas en ingles); 96% tratamiento como prevención; 39% microbicidas vaginales (54% con buena adherencia); 31% una vacuna preventiva y 53-60% circuncisiones médicas en hombres adultos. Para disminuir sustancialmente o eliminar la epidemia del VIH/SIDA en un futuro se necesitara expandir, combinar y aumentar sustancialmente la cubierta de dichos programas.

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