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ANALYSIS & COMMENTARY

The 'Third Wave' Of HIV Prevention: Filling Gaps In Integrated Interventions, Knowledge, And Funding

ABSTRACT There is growing optimism in the global health community that the HIV epidemic can be halted. After decades of relying primarily on behavior change to prevent HIV transmission, a second generation of prevention efforts based on medical or biological interventions such as male circumcision and preexposure prophylaxis—the use of antiretroviral drugs to protect uninfected, at-risk individuals—has shown promising results. This article calls for a third generation of HIV prevention efforts that would integrate behavioral, biological, and structural interventions focused on the social, political, and environmental underpinnings of the epidemic, making use of local epidemiological evidence to target affected populations. In this third wave, global programs should deliver HIV prevention services together with cost-effective interventions for reproductive health and for tuberculosis, malaria, and other diseases. Additionally, new efforts are needed to address gaps in HIV prevention research, evaluation, and implementation. Increased and sustained funding, along with evidence-based allocation of funds, will be necessary to accelerate the decline in new HIV infections.

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Results from recent HIV prevention trials have led scientists to believe that the global decline in HIV incidence can be accelerated. The number of people newly infected with HIV across the world has declined 21 percent since the peak incidence in 1997.[1] Most of this modest decline is attributable to behavior change: the first generation of prevention efforts that included increased condom use, delayed age of first sex, and reductions in numbers of sexual partners.[2] The second generation, biological interventions such as male circumcision and the use of antiretroviral therapy, has also shown great promise.

These approaches can be particularly effective if applied with behavioral interventions and legal reforms. Combination prevention is the term now used to describe the third generation of prevention efforts.

Despite the growing sense of optimism, much progress remains to be made in the fight against the AIDS epidemic. The Joint United Nations Programme on HIV/AIDS (UNAIDS) *World AIDS Day Report 2011* estimated that in 2010, 34 million people were living with AIDS, of whom 6.6 million were receiving treatment, and 1.8 million deaths could be attributed to the disease. Currently, there are 2.7 million new annual HIV infections and only a million new recipients of treatment each year.[3] At this rate, the number of new HIV infections will always remain higher than the number of people receiving treatment. A true turning point in the AIDS epidemic will

occur when more people begin therapy than are newly infected.

There are two ways to achieve this goal: increase the number of people starting therapy, and decrease the number of people becoming infected. Both strategies must be pursued.

Doubling the number of people starting therapy would not be enough to curb the AIDS epidemic; nor would cutting the rate of new infections in half. Massive change is required to get ahead of the epidemic within the next few years. To get there, policy makers everywhere must dramatically intensify prevention efforts and incorporate the entire portfolio of interventions now at hand.

Although effective interventions are needed across the globe, the epicenter of the AIDS epidemic remains in sub-Saharan Africa. The region accounts for 67 percent of the world's thirty-four million people living with AIDS—more than half of whom are still without access to treatment—and the majority of new infections worldwide.[3]

Not intended as a comprehensive review, this article outlines the author's perspective on HIV prevention efforts from three angles: the global response to the epidemic and the evolution of HIV prevention tools; prevailing gaps in HIV prevention research, evaluation, and implementation; and reforms needed for more-effective HIV prevention policies. Principles espoused here provide guidance to the President's Emergency Plan for AIDS Relief (PEPFAR) and other global programs.

Global Response And The Evolution Of HIV Prevention

When future historians reflect on how the world responded to the AIDS epidemic, they will surely describe a protracted but eventually unparalleled global mobilization in response to a health problem. The entire global health system has been radically transformed.

Three salient examples are the creation of UNAIDS, an independent program specifically constituted to address a single disease; the launching of the Global Fund for AIDS, Tuberculosis, and Malaria as a novel funding mechanism; and the creation of PEPFAR by the US government as the largest bilateral health program in history.

Additionally, massive public and private investments fueled the development of new technologies, especially drugs, to combat HIV. People living with the disease created global alliances dedicated to mobilizing an international response—something the world had never seen before. Advocacy and activist groups played key roles in making treatment widely available even though they were at odds at times with donors, scientists, and politicians.

This extraordinary mobilization of resources and efforts has borne fruit. An organized global effort to provide sophisticated antiretroviral therapy in developing countries—something that was dismissed for years as impossible—has resulted in the initiation of therapy by 6.6 million people worldwide.

EARLY RESPONSES AND BEHAVIORAL PREVENTION In 1988 Harvey Fineberg, then the longtime dean of the Harvard School of Public Health, wrote: "Our world has been made a different place by the human immunodeficiency virus. More profoundly, our society is being shaped by our response to the epidemic."[4] He recognized that without a sound understanding of the disease, prevention had to focus on behavioral interventions. And to date, changes in behavior still account for the vast majority of infections averted.

Successful early strategies concentrated on the most affected populations and targeted at-risk groups in the design of prevention campaigns. Concrete examples exist for most continents.

In Mexico the epidemic was initially concentrated among men who have sex with men, commercial sex workers, and paid blood donors.[5] Working closely with those communities, the public health sector took early and aggressive action by providing free condoms and stimulating public debate. Surveillance systems in place flagged a surge of HIV infections among blood recipients and linked it to private blood banks that were reusing intravenous equipment. The Ministry of Health translated evidence into policy with a law prohibiting the purchase of blood products from donors.[6–8]

In Thailand the response to AIDS focused on female sex workers and their clients as main drivers of the local epidemic. Instead of criminalizing prostitution, the government chose to encourage safer sex. A vast public information campaign and the mandating of condom use in brothels had a positive impact on HIV transmission.[9]

In Australia a grassroots campaign was largely led by the homosexual community. AIDS education commercials in that country were initially controversial because of their strong content but turned out to be a successful tool in preventing HIV.[10]

In Senegal political leaders acted quickly when the first HIV cases were identified. They enlisted religious leaders to discuss HIV/AIDS in their services and included education about HIV/AIDS prevention in schools. Because of quick action and the involvement of community leaders, HIV prevalence never reached the high rates

seen in many other African nations.[11]

By the time PEPFAR was launched in 2003, behavioral strategies such as condom use and reduction in numbers of sexual partners had already proved to be successful in HIV prevention. It thus came as a surprise to experts that PEPFAR emphasized an HIV prevention strategy known as "ABC": A for abstinence, B for being faithful, and C for condom use.

The program placed a sizable amount of money in the abstinence component, in spite of the total lack of scientific evidence to support that approach. In its PEPFAR evaluation, the Institute of Medicine recommended "the removal of the limitations imposed by congressional budget allocations for particular activities" in reference to the ABC policy.[12] Fortunately, PEPFAR and other agencies funding HIV prevention have since embraced the need for evidence-based strategies.

As the epidemic progressed, prevention measures in many countries were applied indiscriminately to different target populations—with mixed results at best. In Eastern Europe, for instance, the HIV epidemic is mostly driven by people who inject drugs, but prevention resources have not focused on the affected population groups. Organizations hoping to mount effective behavioral prevention need close collaboration and understanding of the target community.[3]

BIOLOGICAL PREVENTION The discovery of new antiretrovirals in the past decade revolutionized treatment and fueled a second generation of HIV prevention. Following the successes of antiretrovirals for the prevention of mother-to-child transmission and protection of health personnel and others after accidental needle sticks (post-exposure prophylaxis), these drugs have been studied for preventing HIV acquisition in uninfected people, both systemically (preexposure prophylaxis) and topically (vaginal and rectal microbicides). They are also being examined for reduction of transmission of HIV to partners of infected people—a strategy known as treatment as prevention.

The rate of HIV transmission from mother to child has fallen steadily over the past decade. Treatment regimens have evolved in response to evaluation research, and therapy recommended by the latest World Health Organization guidelines[13] is highly effective. Botswana is an example of a country that has successfully implemented programs to prevent mother-to-child transmission. There, free infant formula to women who choose not to breastfeed and a focus on community-based delivery of services have reached more than 95 percent of HIV-positive women.[14]

According to estimates by the World Health Organization, however, fewer than half of HIV-infected pregnant women worldwide currently receive the most effective therapy to safeguard their children.[15] By closing this delivery gap, we could essentially eliminate mother-to-child transmission.

Another promising biological prevention strategy is male circumcision. Two recently published Cochrane Reviews reported on its effectiveness among heterosexuals and men who have sex with men. According to the reports, male circumcision reduces HIV acquisition among heterosexual men by 38–66 percent over twenty-four months.[16] Recent studies from Orange Farm, in South Africa, and from Rakai, Uganda, suggest that the prevention benefit increases over time.[17,18] The results among men who have sex with men are less conclusive, and further studies are needed.[19]

In preexposure prophylaxis, another biological strategy, HIV-negative people at high risk of infection take antiretrovirals to lower their infection risk. Results have been mixed, with some trials reporting positive and others negative results.[20]

In one clinical trial using the antiretroviral microbicide Tenofovir Gel as a prevention method, infection rates declined by 39–54 percent. In contrast, the VOICE (Vaginal and Oral Interventions to Control the Epidemic) study was stopped prematurely because of futility.[21,22] In an attempt to reconcile these results, researchers highlighted lack of adherence as a major barrier to this intervention's success.[20]

In studies of treatment as prevention, placing an HIV-positive partner on antiretroviral therapy earlier in his or her infection lowered the odds of an HIV-negative partner's becoming infected. One study found that when treatment adherence rates were high, the uninfected partner's risk fell by 96 percent.[23]

STRUCTURAL PREVENTION Early in the epidemic, it became clear that transmission of the virus is dependent not only on individual behavior, but also on factors in the social environment that facilitate or impede risky behavior. Structural prevention seeks to understand and remove economic, social, political, and environmental barriers to prevention. Rather than focusing directly on behavior, this strategy seeks to improve the societal context surrounding individuals at risk for infection with the aim of reducing infection rates.

The late Jonathan Mann was a pioneer in advocating human rights as a precondition for effective HIV prevention. During his days at the World Health Organization and later at Harvard University, he initiated a movement to under-

stand the HIV epidemic in the larger social ecology, eventually launching a journal and an academic center at Harvard dedicated to health and human rights.

Early efforts concentrated on human rights such as gender equality, the removal of stigma, and the reduction of intimate partner violence. As the focus of the epidemic shifted to low-income countries and particularly to sub-Saharan Africa, it became clear that conditions of extreme poverty, unemployment, stigma, lack of education, sexual violence, and discrimination create a high-risk environment where people have limited control over their lives.

HIV prevention under these conditions is quite challenging. Broad success will depend on a fundamental shift toward an environment that empowers people who are at risk.

Promising strategies under way include conditional cash transfers as a way of offering incentives for behavioral change such as safer sexual practices. Although many trials of such strategies are still in progress, there are some encouraging results.[24] If conditional cash transfers prove effective in the context of HIV prevention, they would probably be a cost-effective prevention tool.

To date, demonstrating the success of structural prevention has proved difficult. We must improve our ability to determine which structural preventions work and whether and how we can transfer this knowledge to other target populations.

Integrated Prevention Concept

It is clear from looking at different types of prevention that they are often closely linked and interdependent. Biological preventions depend critically on adherence. Widespread HIV testing (on which many prevention strategies depend) continues to be hampered by stigma, and it requires a health infrastructure that can deliver testing services to the target population.

Increasingly, the concept of combination prevention is guiding public health approaches to the epidemic.[25] It assumes that biomedical, behavioral, and structural determinants and outcomes are intertwined and that a combination of all three interventions will have maximum impact on HIV transmission.[26]

The more complex a prevention strategy, the more important it is for public health authorities to tailor it to a particular population, integrating components that have already proved effective among the target group.[26] The most efficient effort will require careful integration rather than just a sequential addition of one strategy after another (Exhibit 1). Thus, it would make sense to refer to the third generation of prevention efforts as "integrated prevention."

Prevailing Gaps

An examination of the global response to AIDS in general and prevention in particular shows that three areas need urgent attention.

RESEARCH GAPS First, there is a research deficit. Current research efforts have proved to be effective in developing new biomedical interventions, and these need to be scaled up with a focus on an effective vaccine and microbicide. However, existing research efforts are not adequate for the development of new behavioral interventions, for using marketing skills that the private sector exploits so well, for learning how to do effective social mobilization, or for changing legal structural barriers.

EVALUATION GAPS Second, current prevention interventions often lack effective evaluation programs. Because of this, it is not fully understood which prevention and treatment programs work best, under what circumstances, and for which populations. Although it is known how much money has been spent globally on AIDS prevention and treatment and how many people are currently under treatment, a good estimate of the number of HIV infections averted through prevention programs worldwide is not available. Integrated prevention programs are particularly in need of careful evaluation, given the complexities of measuring impact from multicomponent interventions.

Some program designs, however, have overcome these difficulties by incorporating stepwise evaluation as various prevention services are rolled out to different parts of the target population at different times. For a largely homogeneous target population, the group awaiting inclusion can serve as the comparison group. An early example is the evaluation of a conditional cash transfer program for poverty reduction based on school attendance and regular health checks in Mexico.[27]

IMPLEMENTATION GAPS Finally, in spite of recent progress, a deficit remains in the delivery of prevention programs to all target populations. To close that gap, an expansion of promising combinations of behavioral, biological, and structural interventions is needed. Bottlenecks to implementation vary from place to place. Most are political, technical, sociocultural, or financial in nature.

With regard to the latter, HIV prevention funding must increase, but so must the efficiency with which it is used to reduce new infections. To justify requests for additional support, prevention strategies must be based on evidence and

EXHIBIT 1

Selected Prevention Strategies And Their Relative Effectiveness

Prevention strategy	Indicator of effectiveness
Abstinence (programs)	Abstinence-only programs do not affect HIV rates in high-income countries[a]
Male condoms	35–94% reduction in transmission[b]
Male circumcision	38–66% reduction in HIV infection over 24 months (for heterosexuals; inconclusive among men who have sex with men)[c]
Microbicides	Study results are inconsistent: 39–54% reduction in HIV infection found in one recent study[d] 0% reduction in HIV infection found in VOICE trials[e]
Needle exchange	18.3–30.9% reduction in HIV infection in cities with needle exchange programs compared to those without program[f]
Preventing mother-to-child transmission	37–77% risk reductions[g]
Preexposure prophylaxis	Study results are inconsistent: 73.1–99.5% risk reduction in HPTN 052[h] 0% risk reduction in VOICE[e]
Treatment as prevention	Relative risk reduction 0.04 (95% CI: 0.00–0.27)[i]

SOURCES See below. **NOTES** VOICE is Vaginal and Oral Interventions to Control the Epidemic study. HPTN is HIV Prevention Trials Network. CI is confidence interval. [a]Underhill K, Montgomery P, Operario D. Sexual abstinence only programmes to prevent HIV infection in high income countries: systematic review. BMJ. 2007;335 (7613):248. [b]Weller SC, Davis-Beaty K. Condom effectiveness in reducing heterosexual HIV transmission. Cochrane Database Syst Rev. 2002;1:CD003255. [c]Note 16 in text. [d]Note 21 in text. [e]Note 22 in text. [f]Hurley SF, Jolley DJ, Kaldor JM. Effectiveness of needle-exchange programmes for prevention of HIV infection. Lancet. 1997;349(9068):1797–800. [g]Orne-Gliemann J, Becquet R, Ekouevi DK, Leroy V, Perez F, Dabis F. Children and HIV/AIDS: from research to policy and action in resource-limited settings. AIDS. 2008;22(7):797–805. [h]Note 23 in text. [i]Anglemyer A, Rutherford GW, Baggaley RC, Egger M, Siegfried N. Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples. Cochrane Database Syst Rev. 2011;8:CD009153.

include ongoing evaluation and demonstration of effectiveness and efficiency. Fund-raising success will depend on factors such as transparency and accountability of money flows; country cofinancing and ownership; and better coordination of multilateral stakeholders, such as the Global Fund, and bilateral stakeholders, such as PEPFAR.

Reforms Needed For More-Effective Prevention Policies

The AIDS epidemic is complex: Different countries have different epidemiological patterns and risk groups, and they face different bottlenecks to prevention. Rather than a "one size fits all" policy, each country's interventions must focus on specific target populations. Yet UNAIDS country coordinators estimate that prevention programs are well matched to the national epidemic in only 10 percent of countries.[28]

Many countries lack monitoring programs and thus do not understand the underlying nature of their own epidemics. Compounding the problem, countries able to use surveillance systems to track their epidemics are often at a loss to understand how best to use national data to create effective prevention programs.[29]

Two important documents released in 2011—the *PEPFAR Prevention Guidance*[30] and the new investment framework from UNAIDS[31]—outline an updated course of action in the fight against HIV/AIDS. The PEPFAR guidelines stress the "Four Knows": the need to "know" or understand the nature of the epidemic in a particular country or region; the need to "know" or understand its context; the need to "know" or understand the existing public health response; and the need to "know" what the associated costs are in order to ensure maximum effectiveness in prevention programs.[30]

The guidelines emphasize that no two HIV epidemics are identical and that therefore it is crucial to tailor prevention programs to the actual epidemic, be it generalized, concentrated in specific populations, or mixed. By knowing where the next thousand cases are most likely to occur, one can evaluate which combination of prevention strategies will be most effective among at-risk populations.

The UNAIDS investment framework proposes a new model focused on three mechanisms: basic program activities; critical enablers—that is, political will, legal reforms, and community mobilization; and synergies with development sectors.[31] Bernhard Schwartländer, director of evidence, strategy, and response at UNAIDS, and colleagues estimate that implementation of the framework would avert 12.2 million new infections and 7.4 million AIDS-related deaths between 2011 and 2020.[32]

Similar to the PEPFAR prevention guidelines,

the UNAIDS investment framework emphasizes the need to determine at-risk groups and direct appropriate integrated prevention programs to them. Proper implementation of the programs outlined in these guidelines would save lives through decreased incidence rates, as well as saving money through averted treatment costs.

Learning From Success And Failure Elsewhere

Although no two epidemics are the same and new knowledge in HIV prevention is needed, there are lessons to be learned from previous successes and failures. Sadly, such learning has not always happened.

For instance, China failed to anticipate the transmission of HIV in blood recipients despite the fact that Mexico had experienced the same problem many years earlier. India failed to anticipate the HIV epidemic in sex workers and their clients, despite Thailand's earlier success in targeting a similar population.

Eastern Europe faces a huge epidemic among intravenous drug users but has failed to incorporate the cumulative experience on effective harm reduction strategies such as needle and syringe exchange programs from countries that have faced similar epidemics. And in Uganda, highly praised for its early successes in battling HIV, legislation that criminalizes same-sex relations threatens to reverse previous gains.

Clearly, there is a need to improve the transfer of knowledge from one setting to another and to incorporate evidence into policy at the highest political level. The disturbing experience with the previous South African government, which actively denied that HIV was the etiological cause of AIDS and resisted the use of antiretrovirals for treatment of HIV-infected citizens, is a reminder of this necessity.

Accountability

Now is the time to invest in HIV prevention and change the course of the epidemic. Recent successes, however, have coincided with the ongoing global economic crisis. Limited funding could impair the implementation of effective integrated prevention. Therefore, accountability through rigorous demonstration that funds are used in the most effective ways is key.

Prevention programs need to become more cost-effective and provide evidence of impact. Countries receiving aid must claim ownership of prevention programs by contributing their own resources. Donors and recipient countries must share responsibility for outcomes, relying on clearly stated goals. Partnerships based on mutual accountability improve program harmony and prevention outcomes.[33]

Diagonal Approach

There has been a long debate in global health as to the best approach to improve population health. The North American culture favors a so-called vertical approach, focused on funding programs for specific diseases and outcomes; PEPFAR is a clear example. In contrast, Europeans are more in favor of "horizontal" approaches that strengthen existing health systems.

An intermediate position is a "diagonal" approach,[34] in which specific health priorities are the drivers of change in the health system. Efforts to prevent HIV/AIDS and both treat and care for those who are suffering should become integrated with cost-effective interventions aimed at other diseases.

For instance, reproductive health, tuberculosis, and malaria are closely linked to HIV/AIDS. Delivering HIV prevention services at the same time, in the same settings, and by the same team of health care providers would produce better results at lower costs than keeping HIV services separate.

This approach would also minimize the additional burden of a stepped-up prevention effort on already stretched health systems. Clearly, for a diagonal approach to be successful, investments in building capacity and strengthening local institutions are fundamental to achieving sustainability.

More And Better Financing

As mentioned, it is not known how many HIV infections have been avoided as the result of ongoing prevention programs. However, if such information were readily available, two conclusions could be drawn. The first is that each HIV infection prevented surely costs more than it should. The reason is that programs frequently apply inefficient mixes of interventions, target them to the wrong populations, and poorly manage their implementation.

The relative efficiency of global funding mechanisms must also be compared. Under what circumstances is it more efficient to channel funds through the Global Fund, through the World Bank, or through bilateral mechanisms such as PEPFAR?

The second conclusion is that not enough is being invested in prevention. Even with current shortcomings, prevention is not only cost-effective but is probably also cost-saving. Each prevented case more than pays for itself in

averted treatment.

Today, with an unprecedented portfolio of prevention tools in hand, additional funding for prevention programs is required. Without a vaccine, prevention of HIV transmission is the only sustainable way to save lives and costs. As estimated recently by Schwartländer and colleagues, $22 billion must be invested annually in order to provide universal access to HIV prevention and treatment by the year 2015.[32] This sum is enormous, but so is the potential impact: 12.2 million new HIV infections averted through the year 2020, 1.9 million of those among children.

PEPFAR, one of the largest HIV donors, supports several pioneering prevention efforts. PEPFAR reauthorization in 2013 by the US Congress will send a clear signal that the world's richest nation, although struggling with an economic crisis, continues its commitment to the global fight against HIV/AIDS.

At this juncture, a turn in the AIDS epidemic seems achievable. PEPFAR has been a major global health force, and it must be reauthorized in 2013. It's also time for other rich and emerging economies to step up to the plate. ■

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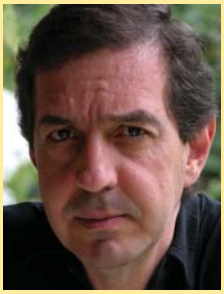

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In this month's *Health Affairs*, Jaime Sepúlveda calls for a "third wave" of HIV prevention, following two earlier ones in which primarily behavioral changes and medical or biological interventions were emphasized. This new wave, he writes, would integrate behavioral, biological, and structural interventions focused on the social, political, and environmental underpinnings of the epidemic, while addressing gaps in HIV prevention research and other areas.

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Previously, Sepúlveda held various senior health posts in the Mexican government, serving for several years as director of the National Institutes of Health of Mexico. Sepúlveda has a medical degree from National Autonomous University of Mexico. He earned a master's degree in public health, a master's degree in tropical medicine, and a doctorate in population science from Harvard University. Sepúlveda is a member of the Institute of Medicine (IOM) and chaired the IOM's PEPFAR evaluation report of 2007. He served as the expert adviser to *Health Affairs* on this thematic issue of the journal, devoted to the President's Emergency Plan for AIDS Relief.