Piecing Together the Prevention Puzzle

Recognizing HIV vaccines as a key component of a comprehensive prevention strategy for young people

August 2013

Made possible by support from:
This report was made possible in part by the generous support of the American people through the United States Agency for International Development (USAID) under Cooperative Agreement No. AID-OAA-A-11-00020. The contents are the responsibility of the Global Youth Coalition on HIV/AIDS and do not necessarily reflect the views of USAID or the United States Government.

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# Table of Contents

Introduction - An HIV vaccine is crucial for young people ...................... 1

Groups of young people particularly vulnerable to HIV .............................. 3
  Young women.......................................................................................... 3
  Young people who are victims of rape...................................................... 4
  Young key affected populations................................................................. 4
  Young people in prison settings.................................................................. 5

Current HIV prevention tools ....................................................................... 6
  Male and female condoms........................................................................... 6
  Treatment as Prevention............................................................................ 7
  Medical male circumcision......................................................................... 9

New Prevention Technologies (NPTs) and young people ............................. 10
  Microbicides............................................................................................. 10
  Pre-Exposure Prophylaxis......................................................................... 11
  HIV Vaccine ............................................................................................ 11

Towards a preventive HIV vaccine for young people ................................... 12
  Challenges with including young people in clinical trials.......................... 13

What can we learn from HPV and HBV trials among young people? .......... 15

The way forward – considerations for planning HIV vaccine trials with adolescents ........................................................................................................ 16

Recommendations for advocates, HIV vaccine researchers and developers, and policy makers ............................................................... 19

Resources and organizations ...................................................................... 21
Introduction - An HIV vaccine is crucial for young people

The best hope for ending the AIDS pandemic is an HIV vaccine. The history of infectious diseases demonstrates that vaccines are one of the most effective public health interventions; diseases such as smallpox, polio, and chickenpox have been eradicated or virtually eradicated through vaccination campaigns. Despite the variety of HIV prevention tools available, such as male and female condoms, treatment as prevention and medical male circumcision, each designed to respond to a different set of circumstances in an individual’s life, there are still two new infections for every person starting HIV treatment. Globally, 39% of these new infections occur among young people aged 15-24. Therefore, a comprehensive HIV prevention package that responds to the specific needs of young people remains a critical global health priority. The current HIV prevention tools have proven to be effective, yet require adherence and behavior change, and the ability to negotiate one’s own protection. Even a 100% efficacious prevention tool will fail to prevent infections among young people if it is not designed to respond to the social, legal, and cultural realities that they face.

Most young people have little or no access to sexual and reproductive health programs that provide them with the accurate information, services, skills, tools, and social support they need to protect themselves from HIV. And if such services are available, their uptake may be limited by legal barriers or policy restrictions related to age, such as not being allowed to have sex under a certain age or services requiring parental consent. When young people under the age of sexual consent do have sex, they have no access to sexual healthcare services, and even risk legal punishment when seeking services. Requiring parental consent creates a barrier for young people who do not want their parents to know that they are sexually active.

Other factors that prevent young people from seeking HIV services is the criminalization of homosexual activities and drug use, services that are not youth friendly including stigmatization by healthcare workers. Due, in part, to such legal and social barriers, less than 20% of young people were tested and counseled the majority of UNAIDS priority countries that are most affected by HIV. These different factors also prohibit access to knowledge and prevention tools. Only 24% of young women and 36% of young men in low and middle-income countries have comprehensive knowledge of HIV. The use of condoms by young people is far from universal, with the majority of countries reporting less than 30-60% use during last intercourse. Young people’s sexual behavior and use of prevention methods are also influenced by social expectations, penalties or rewards for sex, gender roles, and the wishes of their sexual partners. The only HIV prevention tool that protects a young person regardless of his or her authority, knowledge or behavior is a vaccine.
Epidemiological data reveals that young people between the ages of 15-24 are highly vulnerable to HIV. In 2009, 2,500 young people in this age group were newly infected with HIV every day, with 79 per cent of these new infections occurring in sub-Saharan Africa. Two million [1.8 million–2.4 million] adolescents aged 10–19 and 5 million [4.3–6.5 million] young people aged 15-24 were living with HIV in 2010.

This data shows that to halt the HIV epidemic, it is crucial to ensure HIV prevention tools that are not only accessible for young people, but that are also effective in this age group, responding to their specific needs.

According to impact modeling work done by the International HIV vaccine Initiative (IAVI), introducing even a low or medium efficacy vaccine to less than half of the population in a developing country would avert millions of new infections over the course of fifteen years. For example, a vaccine with 50% efficacy given to 30% of the adult population could reduce the number of new HIV infections by nearly 20%. Given the exorbitant costs of lifelong ART, an HIV vaccine would be cost saving, depending on the characteristics of the vaccine and the population coverage. An HIV vaccine could save between US$46 billion to $95 billion in averted costs of ART provision alone between 2020 and 2030 under the current trends in HIV programming. These models are not specific to young people aged 18-24 and do not include the impact of a vaccine if it’s approved for young people under 18. However, it was estimated in 2004 that if a vaccine were approved for use exclusively among adults over 18 years of age, at least twenty five percent of new HIV infections would be missed. In addition, the younger a person gets infected, the more years of treatment will be needed. This means that if a vaccine is approved for young people under the age of 18, even more costs of ART provision can be averted.

From a scientific perspective, there are advantages to focusing on young people in HIV vaccine research, development, and roll out. Responses to other licensed vaccines have shown that immune responses may be more robust and pre-existing immunity to vaccine vectors may be less frequent in younger adolescents than in older populations. For example, fewer hepatitis B virus (HBV) vaccine doses are required in young people to induce a similar immune response as occurs in adults. If this were the case with an HIV vaccine candidate, this could increase efficiency by allowing a reduction in the number of doses given per person if the vaccine is given to young adolescents. HIV vaccine development efforts should therefore consider the age-specific functional responses of the immune system at different stages of maturity.

Young people should be the target population for an HIV vaccine from a social, epidemiological, economic and scientific perspective. A vaccine would effectively respond to the realities that young people face, addressing the gaps that exist with the current HIV prevention tools. But for a vaccine to be approved for young people under the age of 18, they must participate in clinical trials to demonstrate the safety,
immunogenicity, and efficacy for their age group. However, including young people in clinical trials poses particular legal and ethical challenges, which increase research and development costs and decrease the incentive for pharmaceutical companies to invest in the creation of an HIV vaccine that is effective for young people. Advocates, HIV vaccine researchers and developers, and policy makers must work together to prioritize the participation of young people in HIV vaccine clinical trials. Doing so will ensure that the licensure of an HIV vaccine leads to a reduced infection rate for this underserved and disproportionally affected population. **An HIV vaccine for young people has the potential to halt the epidemic.**

Groups of young people particularly vulnerable to HIV

Young women

Every minute, a young woman is newly infected with HIV. Young women disproportionately account for 64% [60–83%] of the young people living with HIV; with HIV/AIDS being the leading cause of death and disease for women aged 15-49 worldwide. The infection rates of young women between ages 15-24 are twice as high as those of young men in this age group, and account for 22% of all new HIV infections worldwide. A young woman aged 15-24 years old is eight times more likely than a young man her age to be HIV positive.

Being concurrently young and female makes young women hyper vulnerable to HIV. They are not always able to negotiate condom use or refuse sex, and often face gender-specific barriers when they want to access sexual and reproductive health programs. As a result of their lower social-cultural and economic status, young women are often unable to receive the information, skills, services, commodities, and social support they need to minimize their exposure to HIV. Transactional and age-disparate sex and sexual coercion, in combination with socioeconomic factors such as inadequate law enforcement, financial insecurity, and weak social and family protection mechanisms increase young women’s vulnerability to HIV. A young woman who is economically dependent on her boyfriend could be up to twice as likely never to use a condom than a young woman whose boyfriend is not her primary source of money. Social gender norms, including violence, also influence HIV incidence. Young women between the ages of 15 and 19 are generally at higher risk of physical and/or sexual violence by a partner than women of older age. A study of intimate partner violence, power inequity, and HIV incidence in young women in South Africa suggested that nearly one in seven cases of young women becoming infected with HIV could have been prevented had they not been subjected to intimate partner violence. In addition to these socioeconomic factors, women are biologically more susceptible becoming infected with HIV through vaginal intercourse than men. This is especially true for young women, whose immature vaginal tracts are more fragile and more likely to tear during sexual intercourse than those of older women.
Many of the barriers preventing young women from protecting themselves from HIV can be overcome with a prevention tool that is controlled by young women themselves without requiring the knowledge of the partner. A vaccine responds to this need and has the advantage of protecting for a longer period of time, meaning that there is no need to initiate the use of a prevention tool prior to unanticipated sexual activity. The availability of a vaccine will ensure that the factors making young women disproportionately vulnerable to HIV, such as gender based violence, the ability to negotiate or refuse sex, and transactional sex will have less influence on HIV incidence. Given the characteristics of the HIV epidemic among young women, a vaccine would have an enormous impact on stopping the growth of the epidemic.

**Young people who are victims of rape**

For between 11 and 45% of adolescent girls worldwide, her first sexual experience is forced. In South Africa, one of the countries most severely affected by HIV, a woman is raped every 17 seconds, and nearly half the victims are under 18 years of age. Trauma and tearing in the genital area makes victims of rape more vulnerable to HIV infection, and there are currently no prevention tools that protect against HIV in the often-unexpected case of rape. Although female condoms, and in the future, microbicides, can be inserted or applied hours before sexual intercourse, they will not offer constant protection if they are not constantly being used. A vaccine is the only prevention tool that offers protection even in cases of sexual violence.

**Young key affected populations**

Young key affected populations—young people who buy and sell sex, young men who have sex with men (MSM), young people who use drugs, and young transgender people—are at higher risk for acquiring HIV than young people of the general population.

Young people belonging to a key affected population carry a double burden: they face legal and social barriers in protecting themselves from HIV because they are young, but their behaviors are criminalized in every circumstance, even if they are above the age of sexual and parental consent.

Factors contributing to the vulnerability of young key affected populations are very context-specific, including stigma, criminalization of their behaviors, and other legal hindrances. These act as barriers for accessing information about HIV and necessary treatment and prevention services. For example, consider the fact that nearly 80 countries around the world have laws that criminalize same-sex relationships, and less than 1 in 10 MSM worldwide have access to HIV prevention services.

Age disaggregated data of young key affected populations and HIV is sparse and varies across regions and within countries, but in many regions of the world young people below the age of 25 constitute a significant percentage of the key
populations who are at a higher risk of contracting HIV. In some countries in Asia, almost half of men who have sex with men and three out of five female sex workers are under 25 years of age. In most Eastern European countries, young people under 25 account for 40% of people who inject drugs. Despite statistics showing that some young people start injecting drugs as young as 12 years old, harm reduction programs are often focused on adults.

HIV prevalence among young key affected populations is often high. In both Tajikistan and Saint Lucia, 12.3% of young people who use drugs are HIV positive. In Indonesia, this figure is 41.5%. In some countries in Africa, such as Guinea-Bissau and Niger, HIV prevalence among young female sex workers is over 20%. Men who have sex with men, and particularly young MSM, are at a higher risk of contracting HIV than the general population, resulting in high HIV prevalence among young MSM. In the Bahamas, for example, 24% of young MSM are living with HIV, compared to 13% in Myanmar and 11% in the Russian Federation.

Despite the demonstrated vulnerability, HIV programs and policies do not currently respond to the specific needs of young people in key affected populations. It is estimated, for example, that in Asia, 90% of prevention resources for young people are targeted towards young people who are at relatively low risk of infection such as in-school youth, despite the fact that the epidemic among young people in the region is mostly concentrated in young key affected populations.

Young people from key affected populations require tailored, accessible prevention and treatment interventions responding to their specific needs and vulnerability as being both young and members of key affected populations.

**Young people in prison settings**

Globally, the prevalence of HIV in prison populations is between two and ten times higher than in the general population, and in some cases it is even as much as 50 times higher. Needle sharing and sexual relationships without the availability of condoms also contribute to these high figures. Young people, especially young women and LGBTQI people, are particularly vulnerable to acquiring HIV in prison. Poor medical and social services, lack of protection for vulnerable prisoners, corruption, stigma, overcrowding and violence contribute to the vulnerability of young prisoners to HIV, among other health risks. Two studies in the US showed that incarcerated young people have lower rates of condom use, a greater number of sex partners, practice anal intercourse more often, and are younger at first intercourse than young people who are not involved in the juvenile justice system. This makes young people in prison more vulnerable to HIV than their non-incarcerated peers.
In a closed setting where young people in particular are highly vulnerable to sexual violence and where condoms or other prevention tools are often unavailable, a vaccine is the only solution to protection.

**Current HIV prevention tools**

*When exploring prevention options for young people, it is crucial to judge their effectiveness based not only on how medically efficacious they have proven to be, but also on whether they are socially realistic and acceptable for young people.*

Even though a wide array of effective prevention tools exists, efforts to implement them have not always been successful. Vulnerability to HIV is affected by structural factors, such as economic, socio-cultural, political, legal and other contextual factors, yet prevention efforts have been largely focused on reducing individual risk. In addition, programs are often siloed in their approach, and do not strengthen each other in achieving the same prevention targets. According to UNAIDS, ‘combination prevention’ (rights-based, evidence-informed, and community-owned programs that use a mix of biomedical, behavioral, and structural interventions, prioritized to meet the current HIV prevention needs of particular individuals and communities) has the best potential to create significant sustained impact on reducing new infections. 37

The HIV prevention tools that are currently available fail to respond to the specific needs of young people and tackle the different barriers that they face in protecting themselves from HIV.

**Male and female condoms**

The male latex condom is currently the most efficient technology available to reduce the sexual transmission of HIV. 38

Knowledge of condoms remains low among young people in high countries with high HIV prevalence, especially among young women. 3

Although male condoms can be up to 98% effective in preventing the sexual transmission of HIV, the majority of countries report 30-60% condom use among young people during last intercourse. 5

Those who use condoms may not use them correctly, and not all condoms are of good quality. Condom use errors are common among many populations, including young people. This includes not leaving space at the tip of the condom, putting the condom on upside down, and not using the condom for the entire duration of intercourse. People also frequently encounter functional problems such as breakage and slippage. 39

Yet it is not only correct use and good quality that are crucial for condoms to be effective. The effectiveness of condoms also depends on the transition of knowledge into behavior change and an increased ability to negotiate condom use.
Relationship dynamics are also an important determinant of condom use among young people. Young women with long-term partners or older partners are less likely to use condoms. Condom use often declines within 3 to 4 weeks in established adolescent relationships, and the partner’s desire for condom use is directly related to the rate of condom use. In addition, willingness to engage in condom-free intercourse is often seen as a sign of trust, therefore, condom negotiation a sign of mistrust. Condom nonuse or discontinuation among young people can also be associated with the idea that condoms reduce sexual pleasure. In addition, carrying or buying condoms can be stigmatizing and embarrassing for young people and is a significant barrier to condom use. The legal age of consent, and thus the legal age to be allowed have sex varies from country to country. Carrying condoms puts young people under the legal age of consent at risk of being charged of being sexually active. And even above the age of legal consent carrying condoms can be dangerous, as one can be charged of prostitution. In several cities in the US, possession of 3 condoms or more is being used as evidence of engaging in prostitution.

Access is another issue that serves as a barrier to condom use. There is a pervasive pattern of stock-outs of both male and female condoms worldwide. In African countries with extremely high HIV burden, the median availability of male condoms is only 9.65 condoms per man per year, with large variations from country to country. The female condom is a strong polyurethane sheath, which is inserted in the vagina and covers the internal and external female genitalia, thereby providing effective protection against HIV.

The greatest advantage of the female condom is that it puts women themselves in control over their sexual health. The female condom is not dependent on male erection and can be inserted up to 8 hours before sexual intercourse. As it does not interrupt sexual spontaneity or sexual pleasure, men have responded favorably to the female condom. Unfortunately, the cost of female condoms is almost 20 times higher than male condoms, and in 2009 there was only one female condom available for every 36 women worldwide. The uptake of the female condom among adolescents is generally low. Young people expressed that unavailability and young women feeling physically uncomfortable inserting the condom were main potential barriers to female condom use.

Even if all other barriers to condom use where eliminated, current levels of condom production, both male and female, simply do not meet the world’s need for this prevention tool. We therefore cannot rely on condoms as the main prevention tool against HIV.

**Treatment as Prevention**

In 2011, a groundbreaking trial proved the efficiency of HIV treatment as prevention. It demonstrated that an HIV-positive person could reduce the risk of transmitting HIV
Young People Need an HIV Vaccine

8

to their uninfected partner by 96% by adhering to an effective antiretroviral therapy (ART) regimen. This is an important breakthrough for people living with HIV and their HIV-negative partners, who have the right to healthy and fulfilling sexual relationships. However, the demonstrated low risk of transmission is probably not realistic outside of trial settings, and low transmission risk can only be reached if the HIV-infected person has access to lifelong treatment without interruptions.

Post-Exposure Prophylaxis (PEP) is a 28-day antiretroviral treatment regimen that, when taken within 72 after potential exposure, reduces the likelihood of getting infected with HIV. The use of PEP is recommended in particular for victims of sexual assault or health care workers. However, PEP is often hard to access. And if PEP is accessible, adherence among victims of sexual assault is often poor.

Despite the effectiveness of ART both as treatment and as prevention (PEP), there are many obstacles that stand in the way of the use of ART as a viable tool for young people.

First, ART is not available or accessible for every young person in need. In 2011, more than 8 million people were receiving ART, while an additional 7 million people were eligible for but did not have access to treatment. There is no age-specific data on young people between the ages of 15-24 who are receiving treatment, yet the global treatment coverage and the fact that countries most affected by HIV report that less than 20% of young people access testing and counseling services suggests that only a limited number of young people living with HIV are receiving treatment.

Another challenge facing young people who are able to access ART is treatment adherence. Studies show that young people can be slow to start ARV after diagnosis, might not have full adherence, often quit treatment, and generally have poorer treatment outcomes than adults. Because of poor adherence, adolescents are less likely to have undetectable viral loads while under treatment, and might have viral rebounds (the virus replicating despite treatment). You people are also more often lost to follow up than their adult counterparts.

ARV pills must be taken every day at the same time for the duration of the patient’s life. It has been found that anything below 95 percent adherence is associated with increases in viral load and drug resistance. Apart from the demanding routine, there are also many psychological challenges that young people face in starting and adhering to ART. Initiating ART can make an HIV diagnosis feel more real and therefore more frightening for young people. They may be forced to disclose their status to loved ones, or they may face the challenge of coping with the illness themselves. Continuing to take the pills daily, manage their side effects, and attend regular follow-up appointments constantly reinforces the reality of being HIV-infected.
To manage adherence issues faced by young people and ensure a low viral load so treatment can also function as prevention, youth friendly care and support is crucial. A study of 287 young HIV positive people in the United States showed that young people who went to an adult HIV clinic, rather than a clinic specializing in care for young people, were twice as likely to quit ARV.\(^8\)

**Medical male circumcision**

Traditional male circumcision is carried out for cultural reasons in many African societies and among ethnic groups in other regions. Medical male circumcision can reduce the risk of HIV infection in men by approximately 60%, when conducted by well-trained health professionals.\(^{64, 65, 66, 67}\)

A recent cost and impact analysis of scaling up medical male circumcision in 14 countries in Eastern and Southern Africa showed that reaching 8% of newborns and males between the ages of 15 and 49 by 2015 would cost $4 billion and could avert 4 million infections. By 2025, this would save over $20 billion in antiretroviral therapy costs.\(^{68}\) According to WHO and UNAIDS, the greatest public health impact will result from prioritizing expansion of male circumcision services for younger males (between the ages of 12-30 years), particularly in high-prevalence settings where there might be a low HIV prevalence among young boys, but they have a high risk of getting infected with HIV in subsequent years.\(^{64}\)

Male circumcision might provide an opportunity to reach male adolescents and young men with sexual and reproductive health services and gender issues.\(^{69}\) WHO recommends that male circumcision delivery should be part of a package of services including HIV testing and counseling, STI’s and promotion of condoms.\(^{70}\)

Acceptability among non-circumcising communities is mostly influenced by concerns about pain, cost and safety. Some traditionally circumcising groups seem to be ready for circumcision services by health care professionals if they are low cost, safe, and do not infringe cultural expectations. However, other groups seem to be reserved to accept medical male circumcision instead of traditional practice.\(^{69}\)

Ensuring that the circumcision practices are safe is key to prevent common complications such as extensive bleeding or infection.\(^{69}\) Cultural practices might increase the risk of (HIV) infection, such as using one single cutting instrument for mass circumcisions\(^{71, 72, 73, 74}\) or the practice of having sex before the wound is fully healed.\(^{69}\)

As it would be preferable to circumcise young boys before they become sexually active, the practice would require parental consent in most settings.
The acceptability of medical male circumcision in both traditional and non-circumcising communities might be a challenge, as well as the health risks involved when the circumcision is not performed in a safe way.

**New Prevention Technologies (NPTs) and young people**

**New Prevention Technologies** are promising tools for young people that could potentially address some of the specific challenges that they face in the use of existing preventions tools. At the moment, research is being conducted on vaginal and rectal microbicides, Pre-Exposure Prophylaxis (PrEP), and vaccines. These new tools can address a critical gap in current HIV prevention options: they do not require the participation of a partner. This is of particular interest for young people, as their use of prevention tools is strongly influenced by their sexual partners.\(^7^5\)

The advantage of a vaccine above other NPTs is that it will offer protection of a long duration after one vaccination or a series of vaccinations, and that it does not have to be initiated before each instance of sexual activity. This responds to the ARV adherence issues of young people and the fact that the decision to have sex is more often unplanned for young people than for older people. It also protects against HIV infection in the case of sexual coercion, which is one of the main factors making young women hyper vulnerable to HIV.

Developing an NPT is a lengthy process that takes many years: from laboratory testing, to safety and efficacy studies and regulatory approval. Approving a NPT for young people, including young people under 18 years of age, is crucial for a NPT to have a significant impact on the global epidemic. For a NPT to be approved for use among young people, young people must be included in clinical trials to assess safety and efficacy among this age group. However, including adolescents in clinical trials poses several social, legal and ethical challenges, such as informed and parental consent and confidentiality.\(^1^2\),\(^7^6\)

**Microbicides**

Microbicides are tools such as gels, creams or vaginal rings, which can be used in the vagina or rectum to reduce the risk of HIV transmission during sex.\(^7^7\) In 2011, there was proof of concept that vaginal microbicides can reduce the risk of women getting infected with HIV through vaginal intercourse.\(^7^8\) The CAPRISA004 trial found that 1% Tenofovir vaginal gel reduced women's infection risk by 39%, when applying the gel 12 hours before and after sexual intercourse. Further research on the effectiveness is currently being done to examine use and effectiveness of 1% Tenofovir vaginal gel, and its potential introduction, as well as a Dapivirine vaginal ring.\(^7^7\) About 5-10% of the world's population, both men and women, engage in anal sex. Unprotected receptive anal sex poses a risk of getting infected with HIV that is 10 to 20 times greater than the risk during unprotected vaginal sex. Different clinical trials are
currently evaluating the rectal safety and acceptability of vaginal microbicides. Gels may work differently in rectal tissue, which requires separate efficacy studies.  

Microbicides cannot be applied far in advance of sexual activity, and must be applied before every sexual encounter, which might be challenging for adolescents, especially in the case of unplanned and inconsistent sex. Identifying products with coital independence will therefore be essential to ensure efficacy in adolescents.  

Multiple efficacy, acceptability and feasibility studies of microbicides have included adolescents from age 14 and higher. A study of “Microbicide safety and acceptability in young men” is currently ongoing and attempts to conduct a behavioral assessment and evaluate rectal microbicide safety and acceptability in young ethnic-minority MSM. The lessons learned from these microbicide trials could inform future trials of other NPTs with young people in terms of how to overcome challenges of the participation of young people in HIV prevention trials.

**Pre-Exposure Prophylaxis**

Pre-Exposure Prophylaxis (PrEP) is the daily oral use of antiretrovirals by HIV-negative people who are at high risk of getting infected with HIV. The FDA has approved the drug Truvada as PrEP in July 2012. To date, three trials have found evidence that Tenofovir-based PrEP can prevent HIV, showing 42%, 62-73%, and 63% reduced risk of HIV infection overall (iPrEx, Partners PrEP, TDF2). Two other studies found no evidence of a reduced risk of HIV infection while on a PrEP regimen. Pre-exposure prophylaxis can offer protection in both young men and women and is not linked to coitus, which could be effective in an age group where social and economic factors make condom negotiation difficult.  

However, adherence is essential to achieving the preventive effect of PrEP, and adherence to prophylaxis pills is often less consistent than adherence to treatment pills. In addition, the implementation of PrEP might be costly, and if an individual does become infected without knowing and continues to use the antiretrovirals, he or she might develop a drug resistance.

The ATN 110 and 113 studies are currently ongoing, and have enrolled young MSM aged 18-22 and 15-18 respectively, assessing safety, adherence, and sexual behavior. The lessons learned from these studies in terms of overcoming legal and social challenges can be of great use for future HIV vaccine trials.

**HIV Vaccine**

An HIV vaccine is the world’s best hope for ending the AIDS pandemic. Unlike other currently existing prevention methods or the other NPTs, a vaccine would be effective regardless of an individual’s behavior or power to use a prevention method. A vaccine could require revaccination, but does not require daily adherence or
initiation of use before sexual intercourse. It would protect against HIV infection in cases of rape and in prisons when condoms are unavailable, and would be a powerful gender equity tool that allows women to protect themselves without a partner's knowledge. However, developing an HIV vaccine has proved extremely difficult. The virus has multiple mechanisms to avoid detection and elimination by the immune system of the body. In addition, different subtypes of HIV circulate in different parts of the world. Depending on the mechanism of a vaccine, it may protect against sexual transmission of HIV but be less effective in preventing blood-borne HIV transmission among injecting drug users.

Scientists are further exploring results of previous HIV vaccine trials by re-boosting clinical trial participants and developing follow-on trials.

The HIV Vaccine Trials Network (HVTN) is currently testing a vaccine concept among men who have sex with men and transgender women aged 18-50 in a Phase IIb efficacy trial. The vaccine concept, known as HVTN 505, is the only ongoing HIV vaccine efficacy trial in the world. The trial has an extensive social science focus, documenting participants' experiences, needs, and attitudes, as well as a strong emphasis on reaching young people of color. Results from this trial are expected in 2013. While this trial does not include young people under 18 years of age, its strong emphasis on young people and their unique needs and vulnerabilities could provide valuable lessons for HIV vaccine trials among young people in the future.

Towards a preventive HIV vaccine for young people

Despite the available HIV prevention tools, HIV disproportionately affects young people and the epidemic continues to grow among people between 15 and 24 years of age. These tools fail to respond to the needs of young people. And although microbicides and PrEP are highly promising tools for young people because they do not require the participation of a partner, the issues of adherence and coital dependence might limit their efficiency among young people. A vaccine is the only HIV prevention tool that, when developed, will truly respond to the issues that make young people particularly vulnerable to HIV.

For an HIV vaccine to be licensed for young people, they must be included in clinical trials that demonstrate safety, immunogenicity and efficacy for their age group. If adolescents are not included in HIV vaccine trials that could lead to licensure, they may not have access to an effective HIV vaccine once it becomes available. Not only would this deny young people an important HIV prevention tool, it would also hamper efforts to stop the AIDS pandemic. Approving an HIV vaccine for adults only means that twenty five percent of new infections will be missed. An important lesson could be learned from the Hepatitis B virus (HBV) vaccine, for which clinical trials to determine safety and efficacy in young people were not conducted until after the vaccine was approved and licensed for adults. The HBV epidemic only began to reverse after the license was extended to young people.
WHO states “the participation of adolescents in vaccine trials would be justified where adolescents may be the target population for vaccines against diseases acquired during or after adolescence, such as HIV, HPV, HSV or other sexually transmitted diseases”.

According to UNAIDS, adolescents should be eligible for enrollment in HIV vaccine trials not only to promote equity, but also because children and adolescents are at high risk of getting infected with HIV. UNAIDS recommends that children and adolescents should be included in clinical trials to ensure safety, immunogenicity and efficacy of the vaccine for their age groups, and that vaccine development programs should address the particular ethical and legal considerations and special needs relevant to adolescent participation in trials.

Despite the fact that 293 HIV vaccine trials have been conducted since 1997, enrolling 60,042 volunteer trial participants, little effort has been made to include people under the age of 18 in these clinical trials. UNAIDS and WHO, as well as numerous advocacy organizations, have made strong statements about the importance of including young people in HIV vaccine trials, and yet there are no HIV vaccine trials that include the participation of adolescents.

**Challenges with including young people in clinical trials**

There are several social, legal, and ethical challenges that prevent the inclusion of young people in HIV vaccine clinical trials, such as parental and informed consent and confidentiality. Due to the stigma and discrimination related to HIV and sexual and risk-associated behavior, trial implementers face the difficult challenge of securing the participation of young people and gaining the approval of their parents/guardians.

In most countries the age of majority, or when an adolescent is considered a legal adult and can consent to his or her own medical treatment, is 18 years old, but globally ranges from 14 to 21. Trial conductors are legally required to include a parent or guardian in the informed consent process if the volunteer is below the age of majority in the host country. However, when adolescents have children themselves, most countries consider them legally mature minors and are able to provide consent for themselves and their child.

Requiring parental consent could significantly decrease young people's willingness to participate in clinical trials. In the case of HIV counseling and testing, removing parental consent can lead to a significant increase of clinic visits and number of HIV tests.

There are diverse reasons for parents to decline participation of their minor in HIV vaccine trials. They may not understand the research protocol, might not interpret
the cost-benefit ratio correctly or may have had negative experiences with the healthcare system or medical research making them question the intention of the investigators. A key concern of parents is the risk of potential harmful effects of participation, such as adverse health effects. Another possible concern is Vaccine-induced seropositivity (VISP), which can lead to what is also known as a “false positive” HIV test that is induced by some HIV vaccines. (10) Parents/guardians might have seen the stigma of a positive HIV test on a family within the community—whether it was discrimination, or an inability to get insurance or a job—and not want VISP to result in unfair ostracization of their children.

Parents have expressed as well that they are afraid that vaccination would lead to unsafe and increased sexual activity—a phenomenon known as “risk compensation”. Focus groups among young people in South Africa revealed concerns of participants that a vaccine would discourage condom use, increase multiple sexual partnerships, and increased the amount of sexual activity. They were also concerned that risk compensation of vaccinated adolescents might increase teenage pregnancy. However, fear of sexually transmitted infections has proven not a major reason for abstinence for young people, and condom availability programs have not been associated with behavioral disinhibition. The Human Papillomavirus (HPV) vaccine, for example, has not been associated with increased sexual activity in vaccine recipients. It is therefore not certain that an HIV vaccine, once available, would lead to increased sexual activity among young people who have been vaccinated.

If community members associate an HIV vaccine with sex or other often stigmatized behavior, parents may fear that trial participation will stigmatize their adolescent children as either sexually active and/or belonging to a sexual minority group or a person who uses drugs. This could potentially lead to discrimination and community isolation. The fear of stigmatization by the community is a concern that is not held by parents alone. A questionnaire among 224 South African adolescents showed that perceptions of what others think, approval and disapproval, and what others expect were of significant influence on the adolescents’ willingness to participate in clinical trials for an HIV vaccine. The willingness to participate was not significantly influenced by knowledge of HIV, attitudes towards HIV/AIDS, or perceived self-risk of acquiring HIV. These findings underline the importance of stigma and the fact that it is crucial to include the community for successful clinical trials and roll out.

Another questionnaire-based study among 240 adolescents in South Africa showed that 52.2% were “definitely willing” to participate in an HIV vaccine clinical trial and 35% were “probably willing.” Important factors influencing their willingness to participate were receiving current information about HIV (88.9%), honoring people who have HIV or have died of AIDS (70.9%), getting free counseling and testing (70.5%), protection against HIV infection (70.2%), and improving motivation to avoid risky behavior (59%). This is valuable information for recruitment and retention strategies, but also shows that clear information must be given about the role of
placebos, and about the fact that vaccine candidates might not protect against HIV.

What can we learn from HPV and HBV trials among young people?

Although the HPV and the HBV vaccine rollouts do not provide perfect models for deployment of an HIV vaccine, there are lessons that can be learned from development, trials, and dissemination that will support the process of developing an HIV vaccine. Although neither HPV nor HBV carry as much stigma as HIV, all can be sexually transmitted. HPV vaccines are targeted to pre-adolescent and adolescent girls, a population that is likely to be a priority for an HIV vaccine, since young women are disproportionately infected with HIV during adolescence. Since both HPV and HIV are linked to sexual behavior, the distribution of the vaccines to young girls implies that the recipient is likely to become sexually active soon, which is a prospect that is anathema to many parents and in many communities. In the United States, the HPV vaccine caused controversy because it associates young and “innocent” girls with sex. The nature of the HPV vaccine was sexualized rather than seen as a preventive vaccine. In addition, many opponents of adolescent immunization of STIs expressed the fear that the vaccine would promote early sexual activity or promiscuity, because the recipients might think they are invincible or that vaccination implicitly gives them permission to have sex. However, a study in which 1,243 girls/women aged 15–24 years responded to questions about receiving the HPV vaccine revealed that HPV vaccination was not associated with being sexually active or with numbers of sexual partners for either 15- to 19-year-olds or 20- to 24-year-olds. In fact, sexually active adolescents aged 15-19 years who were vaccinated were even more likely to always wear a condom than those unvaccinated.

Merck, the maker of the HPV vaccine Gardasil, was the first to face the issues surrounding adolescent participation in HPV vaccine clinical trials. One key difference between HPV and HIV vaccine trials to date is that the young people participating in the HPV trial had to not have had their sexual debut. Merck found a way to avoid directly asking whether a young person is having sex by clearly spelling out in the brochure that the participants had to have never had sex, along with other information about the study. Each person had to check a box indicating that they did or did not want to participate: this “don’t ask, don’t tell” policy avoided potentially awkward conversations and potential participants’ dissembling about sexual debut.

In HIV vaccine trials this is more difficult, as the participants have to be sexually active or planning to soon be sexually active, and behavior would have to be discussed and documented. Merck research staff told parents up front that they would have to leave the room when doctors performed physical exams or discussed sexuality with adolescent volunteers. Parental knowledge and consent was an issue for both the clinical trials and the vaccine rollout. The main marketing strategy for Gardasil was a
mass advocacy campaign designed to spread basic knowledge to the general public about HPV and the vaccine. A key goal was to communicate to parents that HPV can cause fatal cervical cancer, rather than the fact that the virus is sexually transmitted. As Eliav Barr, a Merck physician who oversees trials in youth, said: “The key thing is to educate parents about the disease without emphasizing sexual transmission. Parents will do the world for their children. They just don’t want to think about them having sex.” This was a bigger barrier in the United States than in other countries, for example in Europe, where young people aged 16 and older do not need parental permission to get reproductive and sexual health care.89

Efforts and strategies to introduce HPV vaccines in developing countries could create an infrastructure to deliver an HIV vaccine, as well as other important health interventions for this age group, such as sexual and reproductive health services.105 The hepatitis B vaccine did not engender as much controversy during its roll out as the HPV vaccine. Instead of focusing on one target population, such as young girls, GlaxoSmithKline promoted it as a universal vaccine for all children. By founding the youth HBV vaccine research and marketing on the fact that a child who is exposed to HBV is more likely to develop more aggressive liver cancer than exposed adults, it conveyed a sense of necessity to childhood immunization against HBV. Also, HBV marketing was not targeted towards the general public, but rather to hospital workers and policy makers, who would then individually influence parents and providers.106 The stigma of Hepatitis B is less sexualized than HPV, but the infection is still mainly transmitted either sexually or by sharing needles from intravenous drug use.

HPV and HBV vaccines demonstrate that a variety of strategies may be implemented to avoid eliciting stigma and resistance among parents and communities.

The way forward – considerations for planning HIV vaccine trials with adolescents

For an HIV vaccine to be licensed for adolescent in the future, efforts should start today. This means not only that legal barriers need to be addressed, but that efforts should also respond to the social challenges expressed by young people and their parents in previous studies. These barriers and challenges are context-specific. There is a need for clear understanding of local law and practice, as well as for strategies that address the complexities particular to adolescent participation.93

This section gives recommendations to researchers, advocates and policy makers on the issues to be mindful of when taking steps towards an HIV vaccine for young people.
A cornerstone for including young people in HIV vaccine clinical trials is a youth-friendly approach. It should not be assumed that HIV vaccine clinical trials for the general population would adequately meet the needs of young people. The trials need to be tailored to the specific needs of young people and must be youth-friendly. This means that investigators communicate with young people in a respectful and nonjudgmental manner, that the trial ensures confidentiality and privacy, and that the trial sites have convenient opening hours. It also means that investigators must involve young people in developing policies and implementing services.107

Involving expertise from organizations outside the vaccine field that have experience working with adolescents could be one way to facilitate trials with adolescents.92 In addition, it is key to involve the community to increase acceptability and understanding among community members and avoid stigmatization. This could be accomplished by creating community advisory boards, who can advice on how to set up a trial taking into account the specific needs and cultural norms in the community, as well as creating ownership. It is key that these advisory boards be comprised in part of young people, including young people from key affected populations, to ensure that the trial is designed to adequately respond to the needs of the diverse groups of adolescents.

The informed consent form should be understandable for young people, yet comprehensive enough to clearly explain the concepts, risks and benefits, care provided, and the indemnity for injury arising from the trial. The informed consent process, beginning prior to trial entry and lasting throughout the trial, needs to be adapted to the level of the adolescents’ capacity and understanding.93 In settings where parental consent is required, the informed consent process should also be adapted to the needs of parents to avoid misconceptions that might lead them to disapprove of the participation of their adolescent child.

It is of great importance to protect the privacy of the adolescent trial participant, since his/her personal behaviors when it comes to drug use and unsafe sex will be discussed.89 There may be tension between the scientific urge to want to include a willing adolescent who does not want to open up about his or her sexual history to their parents/guardians and the ethical responsibility to obtain parental consent. HIV vaccine trials should include a package of sexual and reproductive health services. Trials should be seen as an opportunity to reach young people with HIV testing, counseling and education.

Another important consideration for HIV vaccine trials with young people is gender. Trials are often not designed for the complexities of the biology and lives of women. If women are included in clinical trials, numbers of participants are often insufficient to be able to draw statistically significant conclusions about sex differences, resulting in a data gap of safety and efficacy among women. The barriers for women participating in clinical trials include current or future fertility, contraceptives, and
safety for the fetus or for the child when breastfeeding. The fear of stigma when being labeled as being at higher risk for HIV could also be a reason why women choose not to participate in clinical trials. Recruitment and informed consent could be particularly complex for young women, as they might not have the autonomy to decide to participate without their partners’ consent. Being aware of these local gender dynamics, including whether or not a man is allowed to give a vaccine to a woman, are crucial for successfully including young women in clinical trials.

Although it is believed that an HIV vaccine is the best long-term strategy to curb the AIDS epidemic, it is important that the vaccine be well situated within the scale-up of combination prevention. Regardless of the specific groups of young people included in an HIV vaccine trial, HIV prevention should be an integral part of the youth-friendly care and services provided to the young trial volunteers.

Retention methods such as compensation for travel costs and time, or gift cards for health products should be explored in the local context and for different age groups and populations.

The big question is when to start including adolescents in HIV vaccine trials. The FDA suggests that strong safety and immunogenicity data for HIV vaccine candidates should be available for adults before trials start with adolescents. It could be stated that a vaccine should not be tested among adolescents until it has proven to be effective in adults, but this does not take into account the urgency to curb the HIV epidemic. A possible first step could be to enroll older adolescents who are over the age of majority and sexual consent in efficacy trials, and younger volunteers in Phase I and II trials dealing with safety and immunogenicity, which do not require that participants be at high risk of infection. This could potentially deal partially with the stigmatization of young volunteers as being sexually active or engaging in high-risk behavior, and might decrease legal barriers.

There are currently no trials involving young people under the age of 18, but there are trials that involve young people aged 18-24. It is recommended that current and future trials have a stronger focus on the needs, acceptability, and immunogenicity of this age group. While such results cannot simply be extrapolated to young people below 18 years of age, they could offer valuable lessons for future trials that involve young people.

HIV vaccine trials that are currently running or being planned should offer youth friendly informed consent, care and support to trial volunteers aged 18-24. Young people should be involved in shaping the trial to ensure the trial responds to the needs of the young participants.

Best practices and lessons learned should be carefully documented to serve as guidance for trials with adolescents in the future.
Recommendations for advocates, HIV vaccine researchers and developers, and policy makers

An HIV vaccine situated in the scale up of combination prevention has the potential to end the epidemic. For the vaccine to have most impact, it has to be available for young people, addressing their unique vulnerabilities. Taking steps today will ensure timely licensure for adolescents in the future.

Current and planned HIV vaccine trials involving young people aged 18-24

While HIV vaccine trials do not yet include adolescents under 18, valuable lessons could be learned from young trial participants aged 18-24 by having a strong focus on this age group, documenting experiences, needs, acceptability.

Youth friendly informed consent, care and support

Ongoing and future trials should ensure youth friendly informed consent, care and support throughout the whole trial process for young volunteers.

Parental consent

Parental consent could significantly influence an adolescent’s willingness to participate in an HIV vaccine trial. Ensuring the protection of an adolescent’s privacy when it comes to his or her sexual behavior is crucial.

Legal barriers and stigmatization

A possible first step could be to enroll older adolescents who are over the age of majority and sexual consent in efficacy trials, and younger volunteers in Phase I and II trials dealing with safety and immunogenicity which don’t require participants being at high risk of infection. This could potentially deal partially with the stigmatization of young volunteers as being sexually active or engaging in high-risk behavior, and might decrease legal barriers.

Combination prevention and HIV vaccine trials

HIV prevention and sexual and reproductive health should be an integral part of youth friendly care and services provided to young trial volunteers.

Involvement of youth organizations in HIV vaccine development

Youth organizations offer crucial expertise to organizations that are developing HIV vaccines, and should be included in facilitating trials with adolescents.

Community advisory boards

To increase acceptability and understanding among community members and avoid stigmatization, the community should be involved throughout the trial process. This could be done by creating community advisory boards that include young
people including young people from key affected populations,, to ensure that the trial is designed to adequately respond to the needs of the diverse groups of adolescents.

Lessons from HIV prevention trials among young people
HPV, HBV, microbicides and PrEP trials provide important lessons for the development of an HIV vaccine for young people.
Resources and organizations

IAVI - International HIV vaccine Initiative
IAVI is a scientific organization working to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. IAVI conducts research and HIV vaccine trials, advocates for the development of HIV vaccines, and partners with academic, industry, government and non-governmental organizations. They have a lot of background material available, and are welcoming youth organizations to partner with them. IAVI has recently started a partnership with youth organization GYCA.

VaxLit - HIV Vaccine Literacy Initiative
VaxLit is a very useful toolkit including educational materials on HIV vaccines and clinical trials. VaxLit translates complex technical information into simple language.

AVAC – Global Advocacy for HIV Prevention
AVAC is a non-profit organization that uses education, policy analysis, advocacy and a network of global collaborations to accelerate the development and global delivery of HIV vaccines, male circumcision, microbicides, PrEP and other emerging HIV prevention options as part of a comprehensive response to the pandemic. They have a lot of advocacy materials and background information, including simple summaries and explanations about research and trial outcomes. You can also join the advocates’ network.

GYCA – Global Youth Coalition on HIV/AIDS
GYCA is a youth-led global network of over 7,000 young leaders and adult allies working on youth and HIV/AIDS in over 170 countries worldwide. GYCA’s mission is to empower young leaders with the skills, knowledge, resources and opportunities they need to scale up HIV/AIDS interventions amongst their peers. GYCA is very active in advocating for New Prevention Technologies, including vaccines, and has recently started a partnership with IAVI.

ATN - Adolescent Trials Network for HIV/AIDS Interventions
ATN is a research network designed for adolescents and youth between 12 and 24 years of age. The ATN’s primary purpose is to get adolescents included in HIV-related research studies.
Young People Need an HIV Vaccine

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Young People Need an HIV Vaccine  

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