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Youth-Specific Considerations in the Development of PrEP, Microbicide and Vaccine Research Trials

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Abstract

Preventing HIV infection in adolescents and young adults will require a multimodal, targeted approach including individual-directed behavioral risk reduction, community-level structural change, and biomedical interventions to prevent sexual transmission. Trials testing biomedical interventions to prevent HIV transmission will require special attention in this population due to the unique psychosocial as well as physiologic characteristics that differentiate them from older populations. For example, microbicide research will need to consider acceptability, dosing requirements, and co-infection rates that are unique to this population. Pre-exposure prophylaxis studies also will need to consider potential unique psychosocial issues such as sexual disinhibition and acceptability as well as unique pharmacokinetic parameters of antiretroviral agents. Vaccine trials also face unique issues with this population, including attitudes towards vaccines, risks related to false-positive HIV tests related to vaccine, and different immune responses based on more robust immunity. In this paper, we will discuss issues around implementing each of these biomedical prevention modalities in trials among adolescents and young adults to help to guide future successful research targeting this population.

Keywords

Adolescents; youth; biomedical HIV prevention; vaccines; PrEP; microbicides

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Introduction

Significant advances have been made in the treatment of HIV infection over the last decade; however, treatment of HIV infection by itself will not diminish the burden of disease on affected populations. Increased efforts focused on innovative strategies to prevent HIV infection are needed. The HIV prevention toolbox has multiple components (Table 1) and optimal HIV prevention strategies will require a combination of interventions which all have modality-specific considerations specific to youth (Table 2).

Adolescents and young adults represent a highly vulnerable population for the acquisition of HIV infection. The delivery of the majority of HIV prevention strategies will have to be modified due to their dynamic cognitive and physical developmental trajectory. The inclusion of adolescents under the age of 18 in biomedical intervention trials will require significant attention to national, local, and institutional requirements for enrollment of minors into clinical trials. In this review, we raise some additional issues pertinent to adolescent participation in pre-exposure prophylaxis (PrEP), microbicide and vaccine research, outline the challenges, discuss each of the modalities and set the stage for necessary preparatory studies for concurrent licensure of these modalities with that of adult indications.

Adherence Behaviors for PrEP and Microbicides

Adolescence is divided into three developmental time periods: early (11–14 years), middle (15–17 years), and late (18–21 years)[1]. Each of these periods is defined by unique cognitive and physical developmental attributes that are on a continuum. Early adolescence is cognitively dominated by concrete thought processes, with limited ability to comprehend potential consequences of risk behaviors. Middle adolescence is characterized by the emergence of abstract cognitive processes which revert to concrete thinking during stress. The behavioral code is defined by their peer group with major conflict developing between the adolescent and parent as they strive for greater autonomy. Late adolescence is defined by well developed abstract cognitive processing. The peer group is replaced by more adult type close personal relationships. An understanding of this dynamic developmental trajectory is important to contextualize the variety of adherence behaviors youth display when it comes to their health care.

For PrEP to be optimal, plasma levels of the antiretroviral agents should be in a comparable therapeutic range to those for HIV treatment. This requires regular and correct dosing. Pill taking is often less consistent in the setting of prophylaxis[2]. A study of ART adherence in perinatally infected adolescents in the US showed that 25% of the adolescents were non-adherent with adherence significantly associated with self-efficacy and outcome expectancy[3]. For microbicides, identifying products with coital independence will be essential. These concerns over adolescent adherence behaviors will need to be assessed in the setting of clinical trials[2].

Concerns for Disinhibition and Risk Compensation Behaviors

Behavioral disinhibition and risk compensation are important considerations because of the concern that adolescents in a prevention trial will engage in riskier behaviors even if told that the prevention modality being tested is unproven[4]. While these behaviors have not been observed in any ethically conducted adult trials and there are no data to substantiate these concerns for adolescents, more research is required to investigate these phenomena among youth in the setting of blinded randomized placebo controlled trials.

Vaccine-Induced Seropositivity and Youth

Vaccine-induced seropositivity (VIP) is a common concern of individuals participating in HIV vaccine research. Concerns over a "false positive" HIV test are particularly unsettling to younger individuals who may be more likely to undergo routine HIV testing in a variety of contexts. Studies evaluating the extent of potential trial related discrimination and other negative social consequences have generally been reassuring[5, 6]. One of these studies did raise the question of whether younger age may be associated with reporting more negative consequences. The National Institute of Allergy and Infectious Diseases (NIAID) – sponsored HIV Vaccine Trials Network (HVTN) has established a plan for management of such concerns when they may arise in their HIV vaccine research trials among adults[7].

Choice of Drug, Product or Platform

Puberty is associated with significant changes in body fat, muscle mass, and the hormonal environment that may have an impact on biomedical prevention intervention modalities, and more specifically, the types and products that are chosen for study. Body composition changes dramatically during pubertal growth[8]. Age-related changes in drug absorption, distribution, metabolism and clearance may have a significant impact on therapeutic drug levels. It is unclear when the metabolism of medications changes from that of a child to that of an adult. Most drugs are metabolized through hepatic routes, the rates of which can be age-dependent. Differences in phase II drug metabolizing enzymes including glucuronidation, sulfation, and methylation exhibit age-dependent changes[9]. The only mechanism for determining best dosing for adolescents requires intensive pharmacokinetic studies. Cervical ectopy, where the squamo-columnar junction occurs on the ectocervix, is common in young women and may influence STI acquisition[10, 11]. Acquisition of sexually transmitted infections in youth is another consideration for the design of large scale studies of biomedical prevention modalities, whether of vaccines, microbicides or PrEP.

The only drugs currently undergoing PrEP clinical trials are Tenofovir disoproxil fumarate (TDF) with or without emtricitabine (FTC). Limited long-term safety and tolerability data in HIV uninfected adults are encouraging[12]. Some aspects that make this modality more youth-friendly are the ease of administration, long half-life and few noticeable side effects since adherence is a significant issue. These products are likely to have some amount of dependence on timing to the coital act which may also complicate effectiveness. The first trials in adolescents will likely have to be small exploratory studies that determine feasibility, acceptability and safety. One such example is a combination PrEP and behavioral risk reduction study being conducted by the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) discussed later in this article.

Microbicides are in the HIV prevention modality research and development pipeline. Unlike PrEP agents, they have neither the regulatory history nor the extent of human safety data. The safety of some of these products has already been established in adults, but studies in youth are needed. These products will have special considerations for use and timing around the coital act. Further considerations most relevant to youth and unique to microbicides will be the formulation, consistency and ease of delivery of the product as these relate to necessary dosing frequency, product tolerability and other potential mechanical issues upon its application.

HIV vaccines have recently suffered a series of setbacks (AIDSVAX and STEP), prompting the field to regroup. This has resulted in an NIH-supported redirection toward more investment in basic scientific discovery and less focus on large scale efficacy trials[13]. More recently, some encouraging evidence of low-level efficacy was found in a large trial carried out in Thailand[14]. The predominant safety concern after STEP is to ensure long-term safety

and to make certain that risk of HIV acquisition due to the intervention would be minimized as much as possible in subsequent large scale trials. This concern can have one or more biological foundations (i.e. vaccine and/or host related) and it also may have behavioral underpinnings (i.e. trial participants engaging in risk compensation). Vaccines would have fewer adherence or timing of administration considerations once a regimen was received; thus, this modality might hold promise for highest effectiveness among vulnerable youth populations. The recent Thai experience demonstrates the importance of preparing the foundation for inclusion of adolescents in these trials; this preparation includes obtaining important data that would inform and support licensure applications in the context of adolescents.

Pre-Exposure Prophylaxis (PrEP)

A new prevention modality currently undergoing investigation in healthy uninfected volunteers worldwide is PrEP, that of daily or intermittent antiretroviral therapy (ART) given prior to any potential exposure to HIV. Evidence supporting the efficacy of PrEP with ART in decreasing HIV seroconversion derives primarily from experience with post exposure prophylaxis (PEP) using combination ART in animal models[15]. Studies of the pathogenesis of early infection in primate models infected with simian immunodeficiency virus (SIV) suggest that systemic infection does not occur immediately, leaving a brief window of opportunity during which ART may modify or prevent viral replication at the site of infection, specifically in the initial target dendritic-like cells or lymph nodes16. Evidence in humans stems from the well documented reduction of mother to child HIV transmission utilizing ART given to pregnant women and their newborn babies17, 18.

Animal studies of chemoprophylaxis

The most encouraging data suggesting that PrEP may be a potential prevention strategy comes from studies in which monkeys were well-protected from SIV infection after receiving one dose of TDF plus FTC at either 7 days, 3 days, or 2 hours pre-SIV exposure followed by a second dose 2 hours post-exposure[19, 20].

Non-human primate models indicated that FTC/TDF dosing around the time of exposure prevented infection in all animals[19]. These animal models may not be directly relevant to humans because of a number of differences in the infection model: the virus (cell-free SHIV vs. cell free and cell-associated HIV in semen), the host, the circumstances of exposure (atraumatic application of virus in animals vs. sexual intercourse in people), the infectious dose, and the adherence to treatment[20].

Human chemoprophylaxis trials

PrEP would be a welcome addition to the prevention tool box should it be shown to be efficacious. This prevention strategy is not without challenges, however. Although some promise has been shown in animal models, chemoprophylaxis may prove to be ineffective in people because of poor adherence or because HIV transmission is facilitated by disruption of mucosal barriers during sexual intercourse and the presence of virus-expressing cells in semen.

The antiviral agent universally undergoing large scale investigation for this indication is TDF. TDF is a nucleotide reverse transcriptase inhibitor that was originally licensed for the treatment of chronic HIV- 1 infection by the FDA in 2001. In many cases, FTC, a nucleoside reverse transcriptase inhibitor that was licensed for treatment of chronic HIV-1 infection in July 2003, is added to the regimen via a fixed dose co-formulation of FTC 200 mg and TDF 300 mg. This co-formulation was licensed for HIV-1 treatment in August 2004

and is available as single daily pill from Gilead Sciences, Inc. under the trade name "Truvada"[21]. These agents have demonstrated outstanding safety and efficacy in human clinical trials with HIV infected individuals[22]. It is important to note that tenofovir is also effective against Hepatitis B Virus[23], another blood borne and sexually transmitted virus which commonly occurs as a co-infection with HIV[24]. Thus, people who have undiagnosed or untreated hepatitis B may show a hepatitis B viral resurgence or "flare" when stopping PrEP for HIV prevention[25]. Side effects of the drug in HIV infected adults include mostly GI related upsets such as nausea, bloating and mild diarrhea. Toxicity concerns mostly include renal function with creatinine clearance reduction occurring commonly and tubular defects less commonly with a consequent impact on bone metabolism[26]. There is rarely also liver toxicity with steatosis and possible lactic acidosis.

The most robust data to date on the safety and tolerability of these drugs in HIV uninfected adults is derived from a randomized controlled trial conducted by Family Health International in three countries: Nigeria, Ghana and Cameroon in 2005[20]. The study was not completed for political reasons but 859 women were enrolled and showed no increase in adverse event reporting in participants who received TDF daily as compared to those receiving placebo. There are several clinical trials evaluating the efficacy of tenofovir alone or TruvadaR (administered daily) for PrEP ongoing and these multi-center trials are listed in (Table 3). FTC and TDF have similar characteristics suitable for evaluation as chemoprophylaxis. These characteristics include prolonged intracellular half-life that allows once-a-day dosing, high levels of tolerability, potent antiviral effects, and selection of drug-resistant variants that have mutations associated with diminished capacity for replication. Use of two agents for chemoprophylaxis partly increases the activity of the regimen and increases the barrier to drug resistance.

TDF has just recently received FDA approval for use in children 12 years of age and over. The renal and bone metabolism toxicities may be significant for chronic use in healthy adolescents particularly in younger individuals where adverse effects on renal function or bone metabolism may have lasting consequences[27, 28]. Should PrEP prove to be a valid prevention modality, then it may be necessary to consider and test other drugs with similar pharmacodynamic properties to see whether they are safe in HIV uninfected adolescents. Possible candidates may be TMC278 (rilpivirine hydrochloride 25 mg), a new generation non-nucleoside reverse transcriptase inhibitor, currently being developed by Tibotec[29], or one of the new class of drugs, e.g. Raltegravir, an integrase inhibitor developed by Merck30.

Most PrEP studies require participants to take the study drug once a day, similar to treatment requirements. If intermittent or less than daily dosing were effective, it may be easier, more affordable and potentially safer than taking an antiretroviral daily. Intermittent dosing during periods of sexual activity may be more applicable to the adolescent population and may need to be worked into future study designs.

The benefits of including adolescents in PrEP studies

Pre-exposure prophylaxis potentially offers both male and female prevention opportunities, a characteristic that may be important in this age group where social and economic factors may make condom negotiation difficult or impossible and perpetuate coercive or even violent, transactional and transgenerational sex. In addition, a prevention modality that is not linked temporally to coitus may also be more effective in this age group. The first results of PrEP adult studies, IPrEX and the CDC study conducted in Botswana, may be available as soon as late 2010 or early 2011. If PrEP is found to be promising in ongoing trials, it is likely that adolescents will at least need to be enrolled in bridging safety studies only and/or additional efficacy trials. Preparation and planning are required now in order that PrEP trials

can be carried out with adolescents once sufficient data becomes available from current adult trials. Many of the ethical, legal, scientific, socio-behavioral and regulatory issues that complicate the enrolment of adolescents in microbicide and vaccine trials, are likely to impact on PrEP trials with adolescents as well. Additionally, it remains controversial as to whether there is a need to show efficacy before rolling the age for inclusion down to sexually active 16 and 17 year olds.

PrEP research in adolescents

One PrEP preparedness study is ATN 082. This safety, acceptability and feasibility study is currently recruiting in the US with the target of 99 young men who have sex with men (YMSM) aged 18–22 years. After a behavioral prevention intervention, participants are assigned to one of three study arms: daily Truvada, daily placebo or a “no pill” arm. A variety of behavioral and biomedical data are collected every 4 weeks for 24 weeks. This study is specifically intended to evaluate components of a PrEP protocol that might be necessary in a future trial examining the effectiveness of PrEP as a prevention approach for young men who have sex with men (YMSM) at risk for HIV infection. It will also examine the acceptability, feasibility and short-term effects of this combination prevention intervention on sexual risk behaviors among youth. Separate from the main study, qualitative data on the feasibility to future participation in a PrEP study will also be collected from focus groups of younger men whose age excluded them from participating in the study intervention. Thus, this pilot “preparedness” study aims to ultimately obtain the most information possible to inform the design of and build capacity for a future effectiveness study of such an intervention among high risk YMSM populations. The study is being run within the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN), USA[31].

Microbicides

Microbicides are products that can be applied to vaginal or rectal mucosa with the intent of preventing, or at least significantly reducing, the transmission of sexually transmitted infections including HIV-1[32]. The last decade has seen a movement away from the development of broad spectrum microbicide products with relatively non-specific mechanisms of action, such as surfactants, to antiretroviral microbicides that target specific steps in the viral life cycle. Other recent innovations include the development of slow release delivery systems such as vaginal rings impregnated with antiretroviral drugs, improved preclinical evaluation of candidate microbicides, sophisticated multi-compartmental pharmacokinetic characterization of product distribution, and the use of tissue explant systems to provide preliminary data on product efficacy.

Despite these technological advances, fundamental questions remain unanswered about the drug development pathway for microbicides. These include defining the criteria to move products from preclinical to clinical studies, the optimal phase 1 evaluation of candidate microbicides, and whether safety and efficacy data from non human primate (NHP) studies should act as a gate keeper for advancing products into human trials. The effectiveness phase of drug evaluation also remains problematic. In the absence of a robust surrogate for HIV infection, phase 2B/3 microbicide studies require thousands of participants from populations with a high annual seroincidence of HIV infection. The contemporary design of phase 2B/3 studies necessitates inclusion of a comprehensive portfolio of HIV prevention measures including safer sex counseling, diagnosis and treatment of sexually transmitted infections (STIs), provision of male and female condoms, and potentially offering circumcision to male partners. These interventions all lower the risk of acquiring HIV infection and increase the difficulty of demonstrating microbicide efficacy. More recent

challenges include the potential risk of resistance associated with the use of antiretroviral microbicides and the provision of study product once studies have been completed.

The microbicide pipeline

It is estimated that there are approximately 50 candidate microbicides currently in development but only 3–4 in clinical trials (Table 4)[33]. It is unlikely that the majority of these candidates will progress to clinical studies. Many products will fail to demonstrate an adequate preclinical safety / efficacy profile or prove refractory to attempts to formulate the product. Unfortunately, many development teams are simply unable to generate sufficient funds to develop good manufacturing practice (GMP) grade clinical trial material and/or conduct the necessary preclinical toxicology required to undertake subsequent human phase 1 studies.

Design of microbicide trials

Phase 1/2 microbicide studies are used to generate pharmacokinetic and clinical safety data, and may provide preliminary efficacy data. In the absence of a specific safety biomarker, phase 1/2 studies try to use clinical symptoms and signs to identify harm. Unfortunately, in the case of N-9 and cellulose sulfate, this was inadequate and the design of these studies has been expanded to include biomarkers such as cytokines[34]. It has also been argued that the size and duration of current phase 1/2 studies may be inadequate to even identify conventional clinical safety signals[35].

The success or failure of a microbicide is likely to be determined by the complex interaction between product pharmacokinetics, viral kinetics, and possible product induced toxicity[36]. With regard to antiretroviral drugs, there is considerable variability in plasma and genital tract concentration following oral administration[37]. As one example, the cervicovaginal fluid concentration of the CCR5 antagonist maraviroc is almost two fold higher than the blood plasma level[38]. These data emphasize the importance of developing compartmental pharmacokinetic profiles for microbicide candidates that encompass plasma and tissue levels. These assays are technically demanding but are beginning to be included in phase 1 studies.

Phase 2B/3 efficacy studies have been conducted on six microbicides (N-9, C31G, Carraguard, cellulose sulfate, BufferGel, and PRO-2000) without evidence of a significant reduction in HIV incidence39–44. Indeed, the use of N-9 and cellulose sulfate may have increased the risk of HIV acquisition. These very public failures have encouraged some to question the direction of microbicide research45. It is clear that we need to improve the preclinical and phase 1/2 evaluation of candidate microbicides to prevent unsafe products moving into phase 2B/3 evaluation. In addition, it will be important to determine whether the four current microbicides which target HIV reverse transcriptase (tenofovir, UC781, TMC-120, and MIV-150) have sufficiently different safety, efficacy, and PK profiles to warrant moving them all into phase 2B/3 evaluation.

Rectal microbicides

The primary focus of microbicide research has been the development of a safe and effective vaginal microbicide. While this should remain a key scientific priority, emerging epidemiological data provide a rationale for a parallel program to develop rectal microbicides. Since the beginning of the HIV pandemic, men who have sex with men (MSM) have been the main focus of HIV infection in the developed world. Unprotected receptive anal intercourse (URAI) is the primary risk factor for HIV acquisition in MSM. The unique vulnerability of the intestinal mucosa to HIV transmission results in a per act

exposure risk approximately 20 fold greater[46, 47] than unprotected vaginal intercourse. Increasingly, it is apparent that women in both the developed and developing world practice URAI[48, 49]. Although the absolute frequency of URAI in women may be low, the increased risk per act is such that URAI may play an important role in propagating HIV infection in women as well as MSM. Another recent important development is the recognition of sexually active MSM in Sub-Saharan Africa[50]. These men have a high prevalence of HIV infection, often have male and female partners, and may play an important bridging role in disseminating HIV infection. Even with these limited epidemiological data, there is clearly a need for both rectal and vaginal microbicides and even better a product that is safe and effective in both compartments.

In contrast to vaginal microbicide development, the field of rectal microbicide development is relatively new. In some respects this had been advantageous because the field has had the opportunity to incorporate lessons learned from vaginal microbicide development into the preclinical and clinical development of rectal microbicides[51]. Recent phase 1 rectal microbicide studies have incorporated detailed assessment of mucosal injury[52, 53], product distribution[54], and acceptability[55, 56].

There is a need to determine not only the safety of microbicide candidate products, but also whether individuals who may benefit from microbicide availability actually like the products and are willing to use them correctly and consistently. This is generally referred to as acceptability and adherence. Prior acceptability research has identified the main factors to be considered when assessing acceptability. Preliminary research on microbicide acceptability has offered encouraging results. Yet, information is lacking concerning microbicide acceptability in younger populations, particularly minority MSM. Safety, acceptability, and adherence need to be studied concurrently because they affect one another. For example, if a product has little acceptability among potential users (e.g., if they find it too messy, difficult to administer, or uncomfortable), product adherence ("used as prescribed") will be low, which may affect interpretation of data from safety trials.

Enrolling adolescents in microbicide studies is beneficial

The genital tracts of adolescent girls differ biologically from those of adult women and may be more susceptible to HIV acquisition. Different practices and behaviors (e.g. douching) may also render adolescent girls more vulnerable to HIV. All these differences may impact on the effectiveness of candidate microbicides. Consequently, these products will require efficacy testing in both older adolescents, and the sexually active younger adolescents. Adolescent participation in efficacy studies may be challenging, as sexual intercourse may not happen frequently, consistently, or in a planned fashion. If microbicide trials require regular intercourse for the duration of the study, enrollment maybe limited to adolescents with regular partners or those who are sex workers, which may impact on the generalizability of the results.

Adolescents have been included in efficacy, acceptability and feasibility studies of microbicide and microbicide-like products. In a study looking at adolescent reasons for using a microbicide-like product, having a product that did not leak out, that was comfortable and not messy were important characteristics for use57. In a microbicide surrogate acceptability study it was demonstrated that even though participation required parental consent, adolescent girls were recruited with ease, retention over a six month period was reasonable, with two thirds of adolescents reporting use of the product at least once58. Adolescents have been included in microbicide efficacy trials in South Africa (Population Council, Carraguard)[42] and Tanzania and Uganda (Indevus Pharmaceuticals, PRO 2000).

Microbicide trials focused on adolescents

The majority of microbicide trials are conducted in adult women and do not provide insight into the safety, effectiveness, and acceptability of these products in adolescents. From a regulatory perspective, it has been assumed that if a microbicide product was found to be effective in an adult population, small bridging studies could be conducted in adolescents to allow the product indication to be extended to include this population. Two recent studies have attempted to proactively recruit adolescents and young adults into microbicide studies. MTN-004 was a double-blind, placebo-controlled study investigating the safety, tolerability, and systemic absorption of 3% VivaGel^{R} when administered vaginally in healthy, sexually active, young female volunteers twice daily for 14 consecutive days. This study was a collaborative effort between the Microbicide Trials Network (MTN) and the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) funded by the NIH (DAIDS and NICHD respectively). Participants were randomized to either 3% w/w VivaGel^{R}, VivaGel^{R} placebo or the hydroxyethyl cellulose (HEC) placebo gel. The study was completed in late 2009 and will provide a comparison of the safety of VivaGel^{R}, VivaGel^{R} placebo and the HEC placebo gel in sexually active young women.

The second study is an NIH sponsored project entitled “Microbicide safety and acceptability in young men” that attempts to evaluate rectal microbicide safety and acceptability in young ethnic minority MSM in Boston, Pittsburgh, and San Juan. The design is a two-stage longitudinal study (Fig. 1): a clinical and behavioral evaluation (Stage 1A) with an acceptability and adherence trial (Stage 1B), followed by a Phase 1 randomized, double-blind, multi-site, placebo-controlled trial (Stage 2). Participants who complete Stage 1A are eligible to be selected for enrollment into Stage 1B; a similar transition occurs between Stage 1B and Stage 2. During Stage 1B, 120 participants will be given condoms and a placebo gel to use during receptive anal intercourse. Over a three month period they will report the frequency of product use and be interviewed about the acceptability of the product. The first 42 participants who complete Stage 1B with > 80% adherence to product use will be eligible to participate in Stage 2 where they will receive an actual microbicide (UC781) or matched placebo. It is hoped that data from this study will provide unique insights into the acceptability of rectal microbicides in young MSM.

Immune Based Prevention Modalities

Humans are born with a developmentally immature immune system which completes its ontogeny by the onset of adolescence. Adolescents and young adults mount robust immune responses to environmental and microbial antigens and vaccine immunogens exceeding those of young, developmentally immature children, and surpassing those of older adults. These characteristics suggest that adolescents and young adults are an ideal population in which the immunogenicity and efficacy of vaccines to prevent the acquisition of HIV and other sexually transmitted pathogens may be examined.

Causes and Clinical Consequences of Immunological Dysfunction in Early Childhood and in the Aged

The general immaturity of both innate and adaptive immunity in newborns is associated with substantial morbidity and mortality due to bacterial or viral infections (e.g. *S agalactiae (*group B streptococci (GBS)), *E.coli*, Herpes simplex virus or enteroviruses). Until approximately two years of age, children continue to demonstrate poor control of encapsulated bacteria (e.g *Streptococcus pneumoniae, H. influenzae, and Neisseia meningitidis*) and, absent the protection afforded by current vaccines, often develop bacteremia and disseminated infections[59]. In addition, children under the age of 5 years

demonstrate a high rate of extrapulmonary tuberculosis, likely due to a combination of inadequate or ineffective immunological responses that include poor induction of Th1 CD4 T cell responses involved in the clearance of intracellular pathogens[60, 61].

In the elderly, a range of infections is seen which parallels those seen in the first several years of life e.g. Streptococcal pneumonia and septicemia due to GBS and *E.coli* [62, 63]. In addition, there is a high rate of reactivation of viral and bacterial infections that have long been clinically dormant eg tuberculosis and varicella zoster [63, 64].

This age-related diminution in the effectiveness of the immune system (Fig. 2) has been attributed to a progressive reduction in lymphopoiesis, the process in which bone marrow derived precursors differentiate in into B and T lymphocytes. Although murine models and human studies have provided evidence of a reduction in the effectiveness of bone marrow derived precursors with aging[65, 66], the loss of functional thymic tissue seen with aging is also thought to play a substantial role in the loss of T cell production (thymopoiesis). Thymic involution does not occur soon after the onset of puberty, as previously thought. A number of parameters of thymopoiesis have been examined such as quantitative radiographic techniques to examine the size and composition of the thymus, flow cytometric measurement of T cell subsets, and molecular methods to quantify circular DNA molecules generated during the process of T cell receptor gene recombination accompanying T cell differentiation. To date, all show evidence of a steady diminution in thymic function throughout life[67–70]. This loss is gradual, with thymopoiesis continuing into the sixth and seventh decades of life, although at a diminished level[67, 71]. The age-related diminution in T cell generation, coupled with the limited capacity of naïve and memory T cells to divide (replicative senescence) eventually leads to a narrowing of the of T cell receptor repertoire[72, 73].

Clinical data examining immune reconstitution after T cell depletion clearly support the concept of a progressive loss in thymopoiesis. It has been demonstrated that recovery of CD4 T lymphocyte counts after cancer chemotherapy is greater in children and adolescents than young adults[74]. Subsequent studies have also shown differences in T cell immune reconstitution between younger and older women after high dose chemotherapy and autologous peripheral blood stem cell transplantation for breast cancer[75].

These data are also corroborated by examining immune reconstitution of HIV infected individuals during highly active antiretroviral therapy (HAART). Immune reconstitution in HIV infected children generally occurs at a rapid rate, and an early and rapid increase in naïve T cell population represents a major mechanism of reconstitution[76–78]. In adults, immune reconstitution usually begins with an expansion of preexisting memory T cell populations with deleterious effects, known as the immune reconstitution inflammatory syndrome[79, 80]. In contrast, naïve T cells typically emerge in substantial numbers only after adults have received several months of therapy. The completeness of immune reconstitution in adults is substantially influenced by age; HAART is more frequently associated with a restoration of T cell counts to normal range in children than in adults, but young adults have a more satisfactory response than the elderly[80, 81].

As humans age they continuously come in contact with novel antigenic stimuli, producing the possibility of heterologous immunity i.e. immunity to one pathogen due to a previous encounter with epitopes presented in a different pathogen[82, 83]. Unfortunately, there is a propensity of the adaptive cellular and humoral immune responses to target certain immunodominant (preferential) epitopes, which may not be the most effective. Thus, previous immunological experience with one infectious agent might cause the response to a

vaccine antigen to be dominated by previously established T cell clones with suboptimal antiviral activity against the immunogen.

Age-Dependent Vaccine Responses- Adolescents may be ideal to evaluate an HIV vaccine

The age at which maximal cellular and humoral responses to vaccines occurs is unknown, but several examples suggest that optimal responses are made in late childhood, adolescence, and early adulthood. Antibody responses to hepatitis B, inactivated poliovirus, pertussis vaccines, and tetanus and diphtheria toxoids are readily detected in infants, but vaccines composed of bacterial polysaccharides fail to induce the formation of protective antibodies until 18 to 24 months of age59. Seroconversion rates (95–97%) and antibody titers are greatest when varicella vaccine is given between 1 and 12 years of age. In contrast, a lower seroconversion rate (79%) and lower antibody titers are seen with immunization between 13 and 17 years of age[84]. Similarly, antibody titers to all serotypes of HPV present in quadrivalent human papillomavirus vaccine were greater among females aged 9–15 years of age, compared to older adolescents and adults (16 to 26 years of age)85.

At the far end of the spectrum, lower seroconversion rates to influenza and pneumococcal vaccines are seen in the elderly because of the gradual onset of immunological senescence associated with aging[72, 86]. These considerations suggest that adolescents and young adults may be an ideal population in which to study the immunogenicity and efficacy of vaccines for the prevention of HIV infection.

HIV vaccines in efficacy trials for prevention

Few HIV vaccine regimens have been tested for efficacy, and of these only one regimen has demonstrated modest efficacy14. The first efficacy studies tested the VaxGen's AIDSvax, a recombinant form of glycoprotein-120 (gp120) vaccine. This vaccine failed to prevent HIV infection, probably due to the vaccine not inducing broadly neutralizing antibodies87, 88. Two phase IIB trials, the Step study and the HVTN 503/Phambili study, investigating an adenovirus type 5 (Ad5) vector vaccine, the MRKAd5 HIV-1 subtype B gag/pol/nef vaccine, were halted prematurely when the vaccine regimen was shown not to prevent HIV infection, or lower viral load set-point89, 90. In addition, in a post-hoc analysis of the Step study there appeared to be a trend toward a greater number of infections in the vaccine group as compared to placebo. Among vaccine recipients, the risk of HIV-1 infection appeared to be higher in a sub-group of male vaccine recipients who were Ad5 sero-positive or uncircumcised89. The Phambili study, conducted in five sites in South Africa, examined the efficacy of the same vaccine in populations where the predominant circulating sub-type was Clade C. An interim efficacy analysis of this study also showed that the vaccine did not protect against HIV infection90. A recent study conducted in Thailand, in 16, 402 participants using four priming injections of a recombinant canarypox vaccine (ALVAC-HIV) plus two booster injections of a recombinant gp120 subunit vaccine (AIDSVAX) did show a modest benefit with a vaccine efficacy of 31.2%[14].

All of these vaccine regimens have been tested in adults aged 18 years or older; no younger adolescents have participated in a HIV vaccine prevention trial. For most of these trials the relative enrollment among young adults aged 18 and 19 was also quite low. Adolescent enrolment (16–17 years) was proposed for the HVTN 503/Phambili study, before enrollment and vaccination was terminated. This amendment to include adolescents would have occurred after sufficient adult safety and tolerability data had been collected. However, the FDA recommended the delay of adolescent participation in the Phambili study until there was evidence of potential benefit in adults.

HIV vaccines trials in adolescents

Ethical and regulatory issues need to be considered in addition to the scientific reasoning that supports youth enrollment into HIV vaccine clinical trials. The FDA has indicated that before adolescents are enrolled into trials, data on safety and immunogenicity are required from adults[91]. They recommend that adolescent participation should be "stepwise" from older to younger adolescents. (It is unclear at what stage of clinical development the vaccine would be required to be before adolescents are involved)

The FDA has also expressed concern about behavioral disinhibition, or prevention misconception. That is, a person enrolled in a study to test an HIV vaccine that *may* help to prevent disease could mistakenly think that the product *will prevent* disease so that they can safely increase their own risk behavior during a trial. Behavioral disinhibition has not been documented in adults enrolled in HIV vaccine efficacy trials14, [92]. The ATN is currently conducting a trial (ATN 076) evaluating the use of professionally developed, youth-friendly brochures to clarify any misconceptions that youth might have about both the effectiveness of an HIV vaccine and a trial design that includes a vaccine placebo. It is hoped that data accumulated in this study will provide reassurance to the FDA that adolescents can safely be enrolled into HIV vaccine trials.

Trials needed to lay the foundation for licensure in youth

Despite the possibility of extrapolation from selected adult trials, some studies must be done in uninfected, at-risk youth to establish safety, feasibility, acceptability and efficacy in this population. Regardless of the specific agent chosen, pill-taking behavior, possible risk-disinhibition and other behavioral considerations cannot be extrapolated from either adults or HIV-infected adolescents taking these agents as treatment. Appropriate dosing strategies and the necessary social support to maintain adherence must be established in separate adolescent clinical trials. It is time to be conducting preparatory research and designing trials that will pave the way for the inclusion of adolescents in biomedical HIV prevention trials as soon as there is indication that either PrEP, microbicides or vaccines are safe, well tolerated and feasible in adults.

Summary

A comprehensive HIV prevention research portfolio incorporates multiple types of interventions including behavioral modification, voluntary counseling and HIV testing, circumcision, diagnosis and treatment of STIs, vaccines, oral pre and post-exposure prophylaxis, treatment of serodiscordant partners, broader "test and treat" strategies, and microbicides. These various interventions do not exist in isolation and there is a growing interest in integrating multiple modalities into the design of HIV prevention trials[93].

Consequently, a comprehensive, multidimensional prevention strategy for youth will resemble that of adults, with some modifications. In the context of microbicides, there is a need to evaluate the differential safety and efficacy of oral versus topical administration of antiretrovirals for HIV prevention and to explore whether certain high risk populations might benefit from using both routes of administration. A series of important clinical trials evaluating PrEP in diverse adult populations are currently underway globally may yield a better understanding of the safety and efficacy of PrEP as soon as 2011. The HIV vaccine arena has experienced a couple of setbacks, though more encouraging findings were noted in the recent trial conducted in Thailand. Given the robust immune responses seen in youth, this may likely be an ideal population to conduct vaccine trials.

It is necessary to conduct preparatory studies that include safety, feasibility and acceptability among youth if we are to facilitate their inclusion in large scale biomedical prevention trials so that concurrent product licensure can be achieved with those of adult indications.

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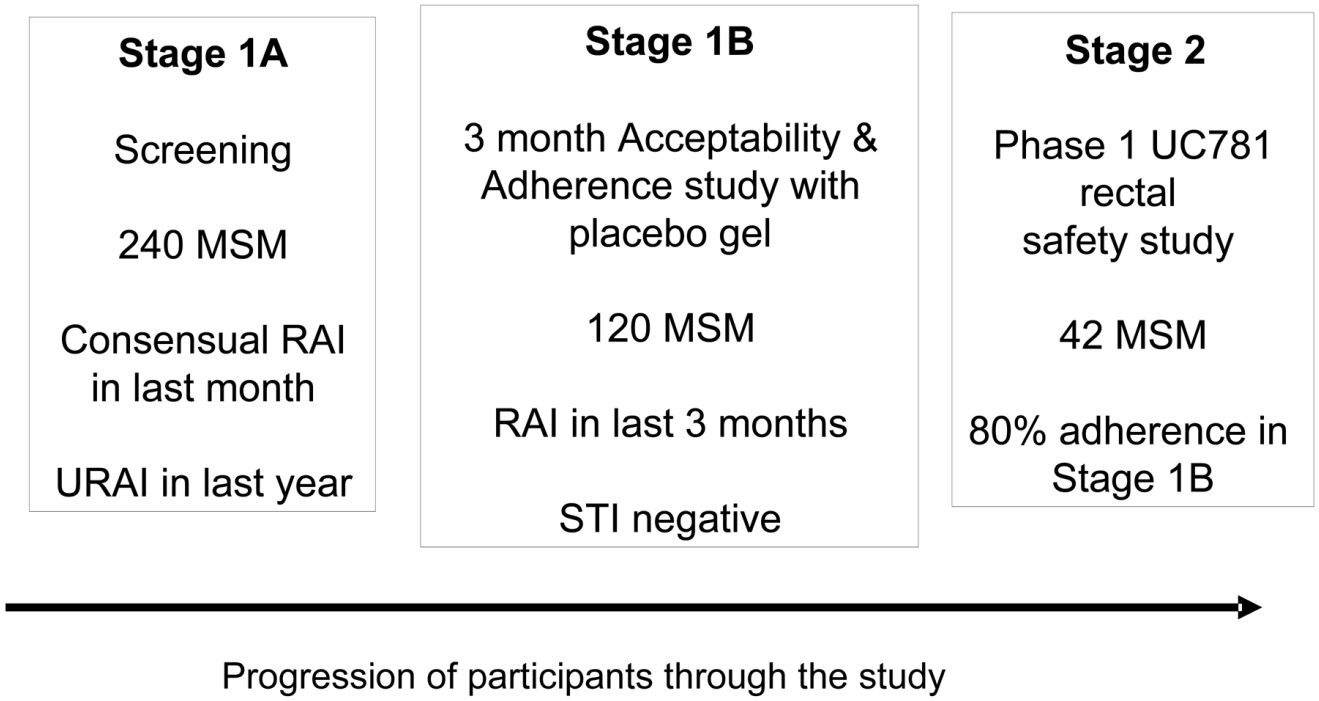

Figure 1.
Phase 1 evaluation of Uc781 gel in young ethnic MSM who have a history of consensual unprotected receptive anal intercourse (RAI). Progression to the evaluation of the UC781 gel is contingent on participants demonstrating ≥ 80% use of placebo product with RAI during Stage 1B.

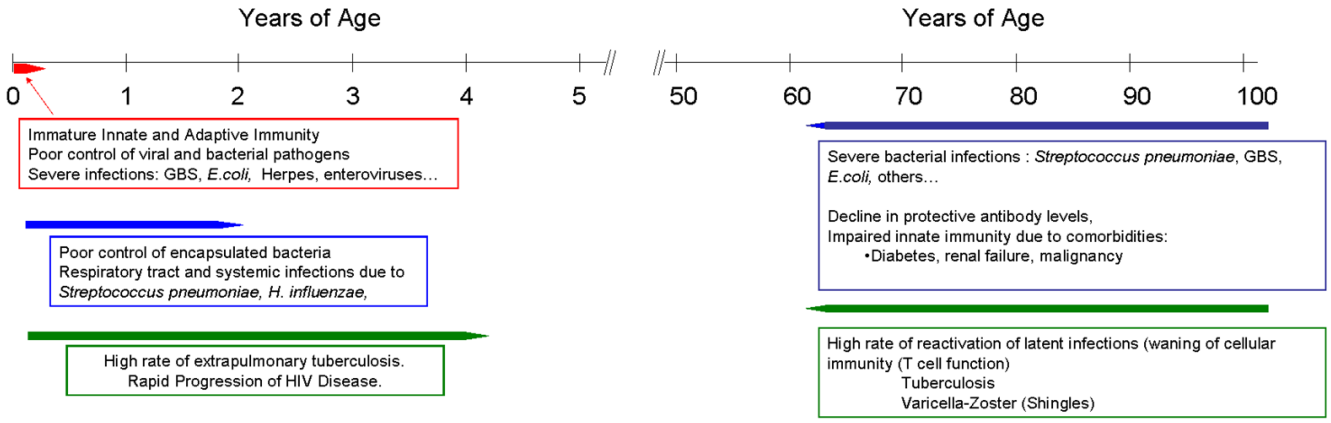

Figure 2.
Age associated infections caused by immaturity or senescence of the immune system

Table 1

The HIV prevention toolbox

Currently available interventions	**Research interventions**
Education	Use of oral antiretrovirals
Partner reduction	Pre-exposure prophylaxis
	Post-exposure prophylaxis
Diagnosis and treatment of sexually transmitted infections	Microbicides
Condoms	Vaginal
	Rectal
Harm reduction (e.g. needle exchange)	HIV Vaccines
Treatment of drug and alcohol abuse	
Circumcision	
Interruption of mother-to-child transmission with antiretrovirals	

Table 2

Overview of Evaluations Needed for Biomedical Interventions to help Prevent HIV among Adolescents

	PrEP	Microbicide	HIV Vaccine
Safety If this modality is safe for adults will it be safe for older (16–17) and younger (10–15) adolescents?	Older-Probably (currently used among HIV infected youth in this population) Younger-May need lower dose to avoid toxicity and lower dose may be effective	Older and Younger- Probably (may have some minor local irritation, but these products are generally very well tolerated).	Older-Probably Younger-May need lower dose to avoid local reaction and lower dose may be effective
Efficacy If this modality works in adults is here a plausible scientific reason to think it may not work as well adolescents if it's used correctly?	No reason it wouldn't work, however adherence issues may decrease effectiveness. Intermittent PrEP may need to be tested as sexual intercourse may not be regular.	It may not work as well among adolescents for biological reasons including: a lack of progesterone in non- ovulatory menstrual cycles that can occur within first several years of menarche, enhanced susceptibility to HIV and other STI infections with cervical ectopy	No reason it wouldn't work; immunogenicity likely to be better among adolescents; long term durability of regimen would need to be ascertained
If this modality "works" in adults, what does that mean?	If used correctly, PrEP could be found to decrease the likelihood of HIV infection by some percentage. Long-term adherence will need to be investigated.	If used correctly, a microbicide could be found to decrease the likelihood of HIV infection by some percentage. Long-term adherence when sex is inconsistent/unplanned will require investigation	If taken properly, a vaccine could be found to decrease the likelihood of HIV infection by some percentage, and/or it may decrease the viral load and the severity of HIV disease in someone who does become infected.
Availability If this modality is approved for use in adults, will adolescents likely have equal access to it?	It may be used "off label" initially in the US. Generic formulations will be needed for use in the developing world.	It may be used "off label" initially in the US. Generic formulations may be needed for use in the developing world.	Vaccines not covered for "off-label" use in US. WHO would likely need demonstrated indication among adolescents in order for it to be recommended and funded.
If this modality is approved for use in adults, how often will it need to be used? (in both adults and adolescents?)	Often	Often	One Series (may need boosting)
	Possibly daily; intermittent PrEP trials are ongoing. Efficacy will depend on adherence.	Will need to be used at least around episodes of sexual activity. Efficacy will depend on adherence.	Will require adherence to a multiple dose vaccine regimen likely within a six- month time frame.

Table 3

Ongoing PrEP trials

Location	Sponsor/Funder	Population (Mode of exposure)	PrEP being tested	Status (Expected completion)	phase
United States	CDC-4323	400 gay men and other men who have sex with men (penile/rectal)	TDF (daily, oral)	Fully enrolled (Q32010)	Phase 2, safety
Thailand	CDC-4370	2400 injecting drug users (parenteral)	TDF (Daily,oral)	Enrolling (Q4,2010)	Phase 2,3 Safety, efficacy
South Africa	CAPRISA, FHI, CONRAD,US AID,LIFElab	900 heterosexual women (vaginal)	Tenofovir 0.1%gel (topical,vaginal)	Fully enrolled (Q3 2010)	Phase 2 Safety and effectiveness
Botswana	CDC-4940	1200 heterosexual men and women (penile and vaginal)	TDF/FTC (switched from TDF Q1 2007) (daily,oral)	Fully enrolled (Q4 2010)	Phase 2 Safety, adherence
Brazil, Ecuador, Peru, US, SA, Thailand (iPrEX Study)	NIH, BMGF	3000 gay men and other men who have sex with men (penile/rectal)	TDF/FTC (Daily,oral)	Fully enrolled (Q4 2010)	Phase 3 Safety and efficacy
Kenya, Uganda (Partners PrEP Study)	BMGF	3900 serodiscordant heterosexual couples (penile and vaginal)	TDF; TDF/FTC (daily oral)	Enrolling (2013)	Phase 3, safety and efficacy
Kenya, Malawi, South Africa, Tanzania (FEM-PrEP)	FHI, USAID	3900 high-risk women (vaginal)	TDF/FTC (daily oral)	Enrolling (2012)	Phase 3 Safety and effectiveness
South Africa; Uganda, Zambia, Zimbabwe (VOICE study)	NIH MTN-003	4200 sexually active women (vaginal)	TDF; TDF/FTC; TDF gel	Enrolling (2013)	Phase 2b Safety and effectiveness
Kenya Uganda	IAVI E001 and E002	150 serodiscordant couples, men and women.	TDF/FTC (daily/intermittent, oral)	Fully enrolled (Q42010)	Phase 1,2 Safety, acceptability, adherence
USA	PrEP in YMSM ATN 082	99 YMSM	TDF/FTC (daily,oral)	Enrolling (2011)	Phase 2, safety, acceptability, adherence
UK	St Stephens AIDS TRust	PrEP using TMC 278LA 100 men and women	TMC278LA (intramuscular)	Enrolling (2011)	Phase 1,2 Safety and Pharmaco-kinetics.

ATN: Adolescent Medicine Trials Network for HIV/AIDS Interventions

BMGF: Bill and Melinda Gates Foundation

CAPRISA: Centre for the AIDS Program of Research in South Africa

CDC: US Centers for Disease Control

FHI: Family Health International

IAVI: International AIDS Vaccine Initiative

MTN: Microbicide Trials Network

USAID: US Agency for International Development

NIH: US National Institute of Health

LA: Long acting

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Table 4

Current microbicide clinical trials

Phase	Drug (s)	Route	Study Title	N	Countries
2B	Tenofovir gel Oral tenofovir Truvada	V/O	MTN-003 (VOICE)	5,000	Malawi , South Africa, Zimbabwe, Zambia, Uganda,
2B	Tenofovir gel	V	CAPRISA-004	980	South Africa
2	Tenofovir gel Oral tenofovir	V/0	MTN-001	144	South Africa, USA, Uganda
1	TMC-120 gel (4759 & 4789)	V	IPM020	180	USA
1	TMC-120 gel (4759)	V	IPM014A	320	Kenya, Malawi, Rwanda, South Africa, Tanzania
1	TMC-120 gel (4789)	V	IPM014B	320	Kenya, Malawi, Rwanda, South Africa, Tanzania
1	TMC-120 ring	V	IPM024	16	Belgium
1	VivaGel	V	MTN-004	61	USA
1	Tenofovir gel	V	MTN-002	16	USA
1	Tenofovir gel	V	NIAID/DAIDS/AECOM	24	USA
1	Tenofovir gel Oral tenofovir	R/O	RMP-02/MTN-006	18	USA
1	Tenofovir gel	R	MTN-007	60	USA
1	Acidform gel	V	AF 020 AECOM	36	USA

Vaginal (V), Oral (O), Rectal (R), International Partnership for Microbicides (IPM), Microbicide Trials Network (MTN), Albert Einstein College of Medicine (AECOM)