The link between HIV & HPV
The acquisition and transmission of HIV is enhanced in the presence of HPV infection implying a plausible reduction in the risk of HIV if an effective HPV preventative strategy is implemented [1]. Reports have suggested the possible relationship between HPV infection and the risk of HIV acquisition, as genital HPV lesions and HIV share risk factors [1]. HIV-infected individuals have a greater propensity for HPV acquisition, and subsequently cervical cancer in women and penile and anal cancers in males. Providing a sexual and reproductive health platform integrating both these diseases seems a logical continuum of care [2].

Linkage studies between HIV/AIDS and cancer registries demonstrate a 2–22-fold increase in incidence of invasive cervical cancer in HIV-positive females compared with the general female population. As the second most common cancer among South African women [3], invasive cervical cancer is inextricably linked to HIV, being regarded as an AIDS-defining condition since 1993 [4,5]. Several independent studies suggest that HIV is independently associated with HPV acquisition and morbidity, but it remains unclear whether HPV infection increases the risk of HIV acquisition [6]. Studies indicate that HIV-infected individuals account for significantly more cervical cytology abnormalities, are more likely to be HPV positive and test positive for HPV types, have greater failure rates postexcisional treatment for precancer lesions and present with invasive cancer at a younger age [1].

Decreased CD4+ (≤200 cells/ul) and abnormal anal and cervical dysplasias are established risk factors in HIV-positive men and women [10]. Data from Rwanda demonstrated this by HIV-negative individuals having a 47% prevalence of HPV versus a 72% persistence in HIV-positive individuals. This was attributed to increased susceptibility, decreased ability to clear infection owing to impaired cell-mediated immunity and reactivation of latent HPV associated with...
immunosuppression [7]. Those HIV-positive individuals were prone to accelerated development of HPV-related cancer [5]. Landmark studies have shown that male circumcision decreases HIV transmission in heterosexual males by 60% and WHO has recommended its addition to current preventative strategies in South Africa, Uganda and Kenya [5,8,9]. Circumcised men are less likely to have prevalent HPV infection, with weak evidence of favorable effects on warts [10].

There are currently limited treatment options for HPV therefore the rationale is to give higher priority to introducing vaccines to populations struggling with higher prevalence of HIV notably sub-Saharan Africa (SSA). Studies have estimated the impact of the HIV vaccine on HPV prevalence and cancer incidence mostly in developed countries with low HIV prevalence. It is critical that developing country models account for high HIV prevalence and the fact that HIV-positive women have a higher risk of cervical cancer [6]. Modeling data from as far back as 1996 has established the potential reduction in endemic HIV prevalence with low efficacy vaccine, albeit at high coverage [11]. These models were substantiated by modeling studies of RV144 showing a significant decline in the proportions of HIV infections when HIV booster vaccinations were made available [12]. In doing so, a partially efficacious HIV vaccine in the context of a high coverage, highly immunogenic HPV vaccine could herald significant reductions in both disease burdens.

### Understanding the global impact of HPV

Epidemiologic studies prove cervical cancer dominates the global burden of HPV related disease [6]. Routine disease burden data of 9–14 year olds is scarcely available but limited survey data alludes to restricted or no access to healthcare with a high untreated disease burden [13]. Trials in adolescents and preadolescents are logistically perplexing considering the extensive follow-up period to accrue sufficient numbers of sexually transmitted infection (STIs) or disease endpoints [14]. Available vaccines afford protection when administered prior to sexual exposure. While adolescents are targeted for immunization, protection is against cervical cancer which peaks in women over 45 years of age [15]. This aspect of HPV pathogenicity represents the model for constructing vaccine-testing strategies, implementing immunization policy, conceptualizing the health economic models and developing strategies for communication on HPV control for the medical community and public [6].

HPV vaccination evaluations conducted among preadolescent females in developed countries show the vaccine to be universally cost-effective, even in the context of existing screening programs [15]. However, while the best evidence would be gauged from adults vaccinated in adolescence (the immunogenicity results in adolescents have been encouraging with the expectation of favorable findings much later on [14]. Thus, cost–effectiveness and impact models have become important. Ministries are often unable to construct these models and rely on analyses from neighboring countries or generic literature-based models. [16]

Vaccine discovery leads to important considerations of costing HPV prevention and medical care within limited financial and human resources, implementing what is theoretically possible and societal norms regarding reproductive health [13]. A major focus of future modeling would be developing countries and effects of vaccination on screening programs [15]. Randomized controlled trials (RCTs) have clearly delineated the high public health value of HPV vaccine interventions. The focus now is to ensure maximally effective and cost-efficient delivery to those most likely to benefit [14].

#### HPV epidemiology

HPV is the most common STI globally. Most sexually active individuals, regardless of gender, will acquire it some point. Transmission is sexual and unimpeded by improved living and health standards [17]. HPV prevalence and age share an inversely proportional relationship globally, with maximal rates seen in women younger than 25 years of age. Infection with high-risk HPV subtypes is recognized as a leading cause of infection-related cancer worldwide, accounting for an estimated 4.8% of total global cancer burden in 2008 (Table 1 [17]). Cervical cancer is the third most common malignancy globally with prevalence fourfold higher in countries with low human development index rank [16,17]. At 88%, HPV represents the leading cause of cancer deaths among women in the developing world [16]. SSA is the only region globally to demonstrate an increase in percentage of cervical cancers reported from 2008 to 2012 (Table 1).
The HPV infection rates in women without cervical lesions are markedly higher in SSA (24%) compared with global estimates (11–12%). There is a greater propensity of HPV presence with increasing severity of cervical pathology, with approximately 90% of women with grade 3 cervical intra-epithelial neoplasia and invasive cancer HPV positive. Sadly, the HPV peak in young women is attributed to the consequence of multiple partners rather than to the natural disease progression – a trait absent in more conservative societies [17]. South Africa has a significant cervical cancer burden (age standardized incidence rate of ∼27 per 100 000) and other HPV-associated malignancies (head and neck tumors), invasive vulval and penile (0.5%) cancers. Industrialized countries are not immune: prevalence in young adult females is reported to be as high as 40–80% with a high lifetime probability of encountering infection (80–90%) [6].

Historically, cervical cytology was the gold standard of cervical cancer prevention with abnormal cytology being referred for colposcopy and treatment. [19] The South African National Guideline for Cervical Cancer Screening Program proposed three Papanicolaou smears from age 30 at 10 year intervals predicting a 64% reduction in cumulative incidence provided widespread coverage is achieved. HIV-infected women have cervical cytology performed at HIV diagnosis and 3 yearly thereafter [20]. However, South Africa’s fragmented health system has repeatedly fallen short on providing a sustainable cervical screening program: it is unethical to provide screening services in the absence of adequate, viable treatment options. Kawonga and Fonn effectively summarized these challenges faced in developing countries as a dire need for reliable screening methods; mechanisms to educate and attract women for screening; validated cytology laboratories; trained personnel to perform screening tests, read and interpret smears; improved communication between service sites and laboratories; systems of follow-up and up-referral in the case of women with precursor

Table 1. Global cancer prevalence attributable to HPV by geographic region (2008–2012).

<table>
<thead>
<tr>
<th>Region</th>
<th>Total number of cancers</th>
<th>Total cases attributable to HPV</th>
<th>Cervix uteri n (%)</th>
<th>Other HPV-associated cancers n (%)</th>
<th>Total number of cancers</th>
<th>Cervix uteri n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>World</td>
<td>12,700,000</td>
<td>610,000</td>
<td>530,000</td>
<td>(4.17)</td>
<td>78,000</td>
<td>13,926,867</td>
</tr>
<tr>
<td>Less developed regions</td>
<td>7,100,000</td>
<td>490,000</td>
<td>450,000</td>
<td>(6.34)</td>
<td>35,800</td>
<td>7,880,972</td>
</tr>
<tr>
<td>More developed regions</td>
<td>5,600,000</td>
<td>120,000</td>
<td>77,000</td>
<td>(1.38)</td>
<td>41,200</td>
<td>6,045,895</td>
</tr>
<tr>
<td>Africa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSA</td>
<td>550,000</td>
<td>78,000</td>
<td>75,000</td>
<td>(13.63)</td>
<td>3160</td>
<td>597,527</td>
</tr>
<tr>
<td>India</td>
<td>950,000</td>
<td>150,000</td>
<td>130,000</td>
<td>(13.68)</td>
<td>12,900</td>
<td>991,276</td>
</tr>
<tr>
<td>America</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central and South America</td>
<td>910,000</td>
<td>75,000</td>
<td>68,000</td>
<td>(7.47)</td>
<td>6480</td>
<td>988,305</td>
</tr>
<tr>
<td>North America</td>
<td>1,600,000</td>
<td>26,000</td>
<td>12,000</td>
<td>(0.75)</td>
<td>13,670</td>
<td>1,775,003</td>
</tr>
<tr>
<td>Europe</td>
<td>3,200,000</td>
<td>80,000</td>
<td>55,000</td>
<td>(1.72)</td>
<td>24,700</td>
<td>3,426,185</td>
</tr>
<tr>
<td>Oceania</td>
<td>130,000</td>
<td>1600</td>
<td>800</td>
<td>(0.62)</td>
<td>&lt;1600</td>
<td>154,376</td>
</tr>
</tbody>
</table>

*Based on data from [17].
†Based on data from [18].
§Include anal, penile, vulval, vaginal and oropharyngeal cancers associated with HPV.
SSA: Sub-Saharan Africa.
lesions or invasive disease; facilities for diagnosis and treatment of precancer and invasive cancer; mechanisms to recall women according to national screening schedules; and continuous monitoring and evaluation systems [21].

Visual inspection with acetic acid (VIA) and HPV DNA testing have been tested as either primary screening tests in combination with cytology or as an adjunct to cytology. VIA has been widely criticized for its poor sensitivity and has been touted as a reasonable alternative to cytology in low-resource settings with poor infrastructure for laboratory-based testing. HPV DNA sampling tested superior to VIA, but the cost remains prohibitive [19]. Lastly, South African studies demonstrate a high level of agreement between physician-collected and self-collected HPV samples tested, highlighting self-collection as a reasonable alternative strategy among adolescents [22].

From as early as 2006, the Program for Appropriate Technology in Health (through support from the Bill and Melinda Gates Foundation, WA, USA) introduced HPV pilot projects in countries such as India, Peru and Uganda. Continued manufacturer donations have ensured HPV vaccination circulation to the likes of Rwanda and Bhutan. The Global Alliance for Vaccines and Immunisation (GAVI) continues to build on this platform with its pledge to support the vaccinations of two million girls by 2015 [23]. Innovative public–private partnerships such as the Pink Ribbon Red Ribbon initiative have built on established President’s Emergency Plan For AIDS Relief-based platforms in Africa and Latin America. The project endeavors to accelerate national implementation strategies for the prevention of women’s cancer thereby reducing cervical cancer mortality by 25% from 2012–2016 among women screened and treated through the program [24].

Primary HPV prevention strategies in developing countries face considerable challenges of competing health demands, poverty, poor educational structures, cultural influences, weakened health systems and financial resources [25]. Studies in Ghana and Botswana identified that educational programs addressing these barriers had the potential to significantly improve HPV vaccine uptake [26,27]. Only global implementation of vaccination and cervical screening practices can offset the emerging HPV endemics and resultant cancer incidence [17].

Clinical concepts regarding the natural history of HPV infection
HPV is a necessary (but not solely sufficient) cause of cervical cancer [28]. HPV is well adapted to infecting epithelia and highly prevalent. It is primarily latent, subclinical and opportunistic for sporadic reproduction and transmission. HPV is generally in quasi-equilibrium with the host [13].

Studies identify wide variation on transmission rates between heterosexual couples. Cervix to anus and anus to cervix autoinoculation among women occurs commonly – whether this serves as a long-term reservoir is unknown. Steady prevalence rates across all ages suggest that in men, unlike women, protection against reinfection does not occur. Males thus have an extremely high cumulative risk of HIV and their risk is associated with sexual behavior [29].

Factors determining infection clearance or persistence are unknown [6]. Anal HPV commonly clears with few developing persistence; an HIV-positive status strongly influences the development of anal neoplasia [29]. Reactivation of latent HPV infection has been reported among sexually inactive HIV-positive women [30]. The protracted lag between peak HPV infection and cancer incidence (between 20–40 years) makes cervical cancer an appropriate target for screening and early detection. Cervical cancer is the end stage of unresolved HPV infection, the persistent presence of HPV DNA in repeated testing of cervical specimens [6].

New infections appear at any age and are benign unless they persist. Half regress within 6 months and the majority (±90%) clear within a few years post acquisition, however no precise definition exists [29]. While not life threatening, anogenital warts are psychologically distressing as it is often refractory to conventional therapy [1,30].

The HPV vaccines
Two vaccines were licensed for prevention of cervical cancer in 2006: a quadrivalent (Gardasil®; Merck & Co, NJ, USA) and a bivalent (Cervarix®; GlaxoSmithKline, UK). Both Cervarix and Gardasil are noninfectious subunit vaccines composed primarily of virus-like particles. Virus-like particles are completely noninfectious and nononcogenic as they lack the viral DNA genome or specific viral genes required for this activity. The HPV vaccines spontaneously self-assemble from 360 copies of L1, a major structural protein of the virion.
Virus-like particle vaccines are based on the concept of forming a structure that sufficiently resembles the outer shell of the authentic HPV virion such that antibodies are induced to react with and inactivate the authentic virus [14]. Both vaccines are considered safe and demonstrate an efficacy exceeding 90% in the prevention of infections caused by oncogenic strains HPV 16 and HPV 18 (estimated to cause 70% of cancer globally) [6,14,31,32]. The quadrivalent provides additional protection against nononcogenic strains HPV 6 and HPV 11. [6,31] The FUTURE I and FUTURE II placebo-controlled RCTs in women aged 16–26 years demonstrated a per-protocol vaccine efficacy of 96% for cervical intra-epithelial neoplasia 1 and 99% for genital warts after an average of 42 months of follow-up [1]. The vaccines display increased immunogenicity, extended duration of protection (approximately 8.4 years to date) and there is a strong indication of ability to induce memory [6,13,14]. There is partial cross-protection against infection and disease caused by a limited number of phylogenetically related nonvaccine types – both vaccines confer protection against HPV 31 and the bivalent confers protection against both HPV 33 and HPV 45 [6,14]. Systematic reviews suggest a waning of this cross-protection with decreased efficacy against persistent infections with increased follow-up [33].

The reduction in disease burden attributable to HPV 16 and HPV 18 may be unapparent for decades [30], but promising USA and Australian data have already demonstrated significant reductions in high-grade cervical lesions, even with their HPV programs in their infancy [34,35]. Trial results demonstrate little geographic variation implying the global validity of the vaccines [6,36]. The quadrivalent vaccine should however result in immediate reduction in genital warts incidence [30]. Gardasil affords protection in excess of 99% against warts in males and females [6]. Australian HPV vaccination programs already reflect a significant decline in number of cases of anogenital warts among females and herd immunity effect in unvaccinated heterosexual men [30].

The vaccines are not without limitations. Widespread vaccine dissemination are restricted by them lacking therapeutic effect, the high cost delaying adoption in developing countries and the limited cross-protection that requires continued screening among those vaccinated [6]. Global donors have pledged support for HPV implementation in 56 of the poorest countries through GAVI. UNICEF is instrumental in procuring and delivery of vaccines in most GAVI eligible countries through technical partnerships with national ministries. Middle-income countries, like South Africa, are ineligible for GAVI assistance and would have to rely on negotiations with manufacturers [16].

- HPV vaccine delivery strategies

Substantive gains in infant immunization coverage, even in developing countries, are poorly reflected in complementary adult HPV screening and treatment strategies [16]. Childhood vaccines being nearly universal makes a promising case for clinical trials evaluating HPV vaccination at younger ages, within existing pediatric vaccination schedules, to increase coverage and decrease the rhetorical possibility of vaccines impacting sexual behavior. The scenario is seemingly plausible as younger children develop more robust immune responses with more durable protection [13]. In South Africa, it provides an additional safeguard against HPV acquisition among sexually abused young girls [37]. Despite the country-specific context, the greatest impact is achieved through universal vaccination of girls prior to exposure [6,31]. Males, however, have a higher probability of HPV infection acquisition than females through increased sexual activity, decreasing ages of first sexual encounter and infrequent condom use [38]. HPV-infected males serve as a HPV reservoir contributing to higher transmission and maintenance of infection among females [39]. The Australian program pioneered male HPV vaccination [40], the CDC now recommends the use of the quadrivalent vaccine in males [41] and Alberta, Canada has most recently introduced the service.

Immunizing young adolescents requires expanding immunization infrastructures to reach largely unattained cohorts. This expansion is challenging. Adding a new vaccine has logistical and cold chain systems implications: the volume of vaccines handled will increase severalfold and cold chain capacity and ability to effectively manage relatively expensive new vaccines warrants system optimization [16]. Infrastructure development or expansion within the national program could deliver services to preadolescents in schools or residency settings without disruption to routine services. HPV could be the stimulus for expanding immunization programs to routinely reach young adolescents for booster doses [16,31].
School-based programs are widely considered the optimal strategy for the HPV vaccine to reach young adolescent populations in developing and industrial worlds. UNICEF reports 84% of children in developed countries attend primary school with an important consideration that boys are more likely to complete than girls [16]. In South Africa, 90% of children are primary-school enrolled, with poor high school enrollment and challenges in reaching adolescents through traditional healthcare reinforcing school-based services is the most practicable option [31]. HPV vaccination introduction studies in Rwandan schools boasted 96% vaccine coverage of 11 year olds. Cooperation between education and immunization departments is pivotal to such success. The South African reintroduction of the Integrated School Health Program, based on WHO guidelines, makes provision for on-site services focusing on sexual and reproductive health from Grades 4–12 [31]. Comprehensive counseling would encompass diverse adolescent concerns from alcohol and drug use, smoking, diet, emotional issues, school or family issues to bullying [16]. In 2006 the Program for Appropriate Technology in Health initiated formative research and demonstration projects in India, Peru, Uganda and Vietnam testing delivery strategies in schools, health facilities or community outreach [6]. Sustainable projects in schools of industrial and developing countries provided validation that high coverage can be achieved and that programs were acceptable to parents. GAVI-eligible countries have garnered the financial support of global donors for HPV vaccination. Middle-income countries not eligible for GAVI support would have to negotiate regional bulk-buying schemes to improve affordability of the vaccines [16].

The growing concern among parents, given the sexual transmission nature of HPV, that the vaccine would be misconstrued as endorsing premarital sex was conjecture, invalidated by studies in Peru, Uganda and Vietnam [6,16]. In fact, progress in societies hinges on the fact that HPV prevention and care does not unleash promiscuity but enhances the worth of life and health. This however remains a dilemma for political leaders who appear to ‘challenge’ parental autonomy, in advocating for sexual health among preadolescents [13]. There is a grave disjuncture between media and pop culture that glamorizes sexuality versus the need for candid, open discussion about sexual health and impact of STIs [13]. In the developing world, most displayed poor knowledge on HPV causing cervical cancer; many were aware of cervical cancer due to the high prevalence and showed concern about it. Studies show that parents knowledgeable about HPV were more likely to accept the vaccine and allow immunization of their girls. Many conservative cultures have been reluctant to vaccinate adolescents, preferring vaccination prior to marriage. Research however shows that parents still believe their children engage in sexual activities which favors early vaccination [16]. Logical concerns raised by parents include effect on fertility, safety, effectiveness and accessibility [6,16].

Current evidence of health economic analyses call for female-only immunization in the developing world [16]. Even in developed countries, there remains a stark contrast between the intention to be vaccinated and initiating vaccination with many women aged between 16 and 26 years identifying barriers such as cost and poor knowledge. Intention to vaccinate was linked to sexual experience - those without the intention to vaccinate had never been sexually active, do not perceive the risk of HPV and did not feel they need the vaccine. These findings suggest the need for comprehensive communication regarding the lifetime risk of HPV and need to ensure vaccination prior to the initiation of sexual activity [42,43].

Understanding the global impact of HIV

The South African government has endeavored to halve HIV incidence by 2014 [44,45]. The national response is rapid HIV testing as a screening and diagnostic tool [46]. Already in place is Prevention of Mother to Child Transmission, a vertical program with the capacity to save approximately 37,000 newborn lives annually if effectively implemented [44]. Male medical circumcision is widely regarded as the most efficacious epidemiologically and cost-effective measure [47,48]. Recommendations for implementation are based on the proven efficacy exceeding 60% on three landmark RCTs [48]. Despite this, implementation remains complex and challenging. South Africa has arguably the largest national antiretroviral therapy (ART) roll-out program in the world. Scaling up financial resource allocation to meet ART demands will prove challenging [49]. These exorbitant, escalating costs underpin the potency of a HIV vaccine as a primary preventative strategy.

There has been no documented adolescents aged <18 years participating in HIV vaccine trials to date, with a limited number involved in microbicidal trials and HPV vaccine trials [50].
This is despite the most vastly affected SSA countries reporting adolescent female (15–24 years) infection rates eight times higher than their male counterparts attributable to a host of behavioral and biological factors [51]. Vaccine efficacy has yet to be demonstrated through RCTs in South Africa. Involvement of adolescents through bridging studies will hopefully allow for the rapid implementation of HIV vaccines in this population [50]. South African law does not explicitly prohibit adolescent clinical trial participation provided that their constitutional rights are not infringed upon, in other words their best interests are maintained [52]. The law is circumspect in that adolescents do not have the individual capacity to participate in medical research often requiring parental consent from both parents, legal guardian or parental consent to all forms of research or parental consent with adolescent assent [53,53].

Adolescent willingness to participate in vaccine trials has been demonstrated, especially following the premature discontinuation of the HVTN 503/Phambili HIV vaccine trial [54]. Various such studies have addressed barriers to enrolment in this group including HIV testing, stigmatization post-testing, mistrust of the health system and concerns around sexual disinhibition [54,55]. Theoretically, urgent adolescent inclusion in HIV vaccine preventative trials has been welcomed from all sectors [56–58]. The practical application thereof requires painstaking qualification and safety is a major concern. The lack of efficacy of current microbicide trials and the futility of adenovirus 5 (Ad5)-based HIV vaccines suggests that testing on adolescents may be premature and a greater wealth of information may be gauged from rapid bridging studies. Concerns ranged broadly from involvement of adolescents only once safety had been established among adults and parental and cultural acceptability of the vaccines, to fears of sexual disinhibition and fears of HIV testing and disclosure [56,57].

There have been noteworthy applications of HIV vaccines in those aged 15–29 years using mathematical modeling studies [59]. Mathematical modeling has also been widely used to explore the effects of HIV-prevention models in several populations looking at feasibility, cost–effectiveness and overall impact on disease burden [60–63].

- HIV epidemiology

Evidence suggests an almost 20% reduction in HIV incidence globally, except among key populations in Eastern Europe and Central Asia (intravenous drug users) and Asia, America and Africa (men having sex with men) and persistent sexually transmitted epidemics among young women and girls in SSA [64]. Youths aged 15–24 years in SSA face the highest risk of HIV acquisition. By the end of 2011, 0.8% of the 34 million people living with HIV globally belonged to the reproductive age group. [65] These figures are jointly encouraging but discouraging, as the disproportionate concentration of the worldwide epidemic remains seated in Africa with female predominance (the only place globally) and highest rate among young women and adolescents [66,66]. In SSA, women acquire HIV in their early teenage years, at least 5–7 years prior to males who contract disease in their mid-20s. Early and considerably higher rates (at least eight-times higher) female acquisition continues to fuel the SSA epidemic [64].

The South African HIV epidemic is well documented as generalized, predominantly driven by sexual transmission, estimated to account for 16.2% of the global HIV prevalence [67] and sharing a similar global epidemiological trend with adolescents being exceedingly vulnerable to infection [68]. HIV prevalence among 15–19 year olds has steadily risen from 2.4% (1990s) to 14.1% currently [64]. South Africa has the greatest burgeoning HIV burden, with 21% of females and 5% of males acquiring HIV by 24 years of age, hence the exigent need for prevention strategies [69]. The epidemic can only be controlled by breaking the transmission cycle in females through prevention [64]. Adolescent women in this setting are invariably prone to higher HIV rates, unplanned pregnancies and development of STIs [70]. There are no therapeutic or prophylactic trials that include adolescents in or out of schools examining the prevention of sexual transmission of HIV using ARV. The implication of adult prevention measures on youth is unclear as they are behaviorally and socially different [71]. South African adolescents highlight the need for targeted and vigorous interventions at a local level, together with continued efforts to enhance HIV-preventive options for marginalized and inaccessible groups [64].

Many youth have not sexually debuted; early interventions may be effective for establishing or reinforcing safer sexual behavior in these formative years. Timing and optimal delivery methods still remain unanswered though. South African youth have often reported stigmatization
Clinical concepts regarding the natural history of HIV infection

Primary HIV infection is characterized by transient symptomatic illness in 40–90% of individuals, associated with high levels of viral replication. HIV-specific immune response lacks efficacy during early stages of HIV spreading during primary infection \[73\]. Antibodies are produced by the B lymphocytes of the immune system. Receptors found on the surface of each circulating B cell are unique, enabling an immune response to any foreign structure. B cells meet an antigen (foreign entity) that matches its receptors and is stimulated to proliferate and secrete antibodies against the structure. B-cell genes frequently undergo somatic mutation (nongermline) to increase the affinity of the antibodies they produce. HIV antibodies are unusual in that they are highly somatically mutated which means they are different to those evaded by B cells initially responding to infection \[74\].

Infected individuals present with nonspecific symptoms of fever, fatigue, rash and lymphadenopathy. The symptomatic phase lasts 2–4 weeks in individuals with normal rate of disease progression, whereas severe and prolonged symptoms are associated with rapid disease progression. Once chronic disease has been established, the course is determined by substantial influence of host (genetic and immunological) or virological factors. HIV-specific antibodies appear to have limited efficacy in control of virus replication during chronic infection \[73\]. Some patients infected with HIV (10–30%) develop broadly neutralizing antibodies (bNAb) late in natural infection (~2–4 years postinfection) \[74,75\].

High level somatic mutation is required to produce bNAb. Under normal circumstances the high affinity of an antibody for its target is achieved usually after 10–15 mutations in the complementarity-determining region of the antibody that forms with antigen contact site. However potent bNAb contain 40–100 somatic mutations spanning both the complementarity-determining region and constant mutation resistance framework region. This is the molecular basis for the bNAb taking 2–4 years to develop \[74\]. There have been no reports of spontaneous, immunologically driven clearance of HIV following infection \[73\]. Latent HIV reservoirs are established secondary to the death of the operational immune response \[73\].

Two specific groups bear mentioning. Long term nonprogressors account for 1–5% of HIV infected and experience stable disease, lack of decline in CD4+ T-cell counts and control of virus replication <100 HIV RNA copies/ml for extended periods (at least 7–10 years) in the absence of ARV. Elite controllers (<1% of HIV infected) show control of virus replication <50 RNA copies/ml regardless of time of control \[73\].

A new dimension of the eradication agenda suggests that CD8+ T-cell responses are critical for attempts to purge virus-infected cells following activation of latent reservoir. Studies of elite controllers show specific qualities of CD8+ T cells highly desirable in a vaccine; they inhibit viral replication \textit{ex vivo}, deliver cytotoxic granules to HIV-infected target cells and exhibit multiple effector functions at the same time (polyfunctionality). CD8+ T cells from elite controllers are cross reactive (recognizing viral variation and mutations), and preferentially target more conserved and vulnerable parts of the HIV \[75\].

HIV vaccines

The tremendous genetic diversity of global circulating strains of HIV-1 has long been the bane of vaccine-mediated protection. HIV-1 is able to elude the immune response through mutational escape and constant viral evolution within the population and in individual hosts. The diversity complicates designing a HIV-1 vaccine that will be immunologically relevant in the face of a variety of HIV sequences \[76,77\]. Stephenson and Barouch outlined four potential strategies for the development of a global HIV vaccine: design geographically specific vaccines that encompass tailor-made antigens to match circulating HIV-1 strains; design a vaccine that elicits Env-specific antibodies capable of broadly neutralizing all HIV-1 subtypes; vaccines that will elicit cellular immune responses that are focused on highly conserved HIV-1 sequences; and vaccines that elicit highly diverse HIV-1-specific responses \[77\].

The Thailand trial RV144 evaluated four priming injections of recombinant canarypox vector vaccine (ALVAC-HIV[vCP1521]) plus two booster injections of recombinant glycoprotein 120 subunit vaccine (AIDSVAX B/E). Many trials of
subtype B canarypox vector primes and boosters containing subunit gp120 or 160 established the prime-boost concept as a candidate for further testing. Canarypox prime-boost regimens induced humoral and cell-mediated immunity, but CD8+ on ELISA was low and the presence of primary isolate neutralizing antibodies was not consistently detected [78]. Promising data from RV144 showing antibody response and protection identified in human trials [78] revitalized the quest for an antibody-based HIV vaccine [79]. RV144 offered 31% protection against HIV-1 acquisition. While the protection was moderate and transient, it was nonetheless significant enough to be considered for improving the RV144 vaccine regimen for licensure in high-risk populations. Vaccine efficacy did decline from 60% (year 1) to 31% (year 3.5) raising the question of whether increasing the number of boosters might improve vaccine efficacy. Importantly, the Thailand trial vaccine was well tolerated and elicited durable cell-mediated immunity and humoral immune response. Follow-up studies on ALVAC vectors and gp120 proteins are envisaged with subtype C immunogens for future clinical trials in South Africa [77].

STEP (Americas, Caribbean and Australia) and Phambili (South Africa) evaluated Merck’s Trivalent Ad5-HIV-1 vaccine in high-risk men who have sex with men, heterosexual men and women in Australia and predominantly heterosexual men and women in South Africa [79,80]. The STEP trial found that 41% vaccinees developed HIV-specific CD4+ cells (potential to support and maintain long-term antiviral CD8+ T-cell memory) and only 31% mounted CD4+ and CD8+ HIV-specific T cells [75,81]. STEP was terminated prematurely in 2007 on the grounds of futility. The vaccine failed to prevent infection or impact on early viremia but did induce a T-cell response of magnitude to similar trials before [81,82]. Ad5 as a vaccine vector has been under scrutiny due to a non-significant trend for higher HIV-1 infections in vaccinees with pre-existing Ad5 specific neutralizing antibodies. Phambili was then suspended, followed by HVTN 505, for futility in 2013 – both involved Ad5 vector HIV1 vaccine [79]. Post hoc multivariate analyses of STEP participants showed an increase in HIV among vaccinees was accounted for largely by uncircumcised males and/or pre-existing Ad5-specific humoral immunity [82]. Highly effective HIV-1 vaccines will need to harness T and B cell immunity to protect virions and virus-infected cells [83]. Memory cells of low antigen states persist longer, show lower degree of senescence and higher proliferative capacity, therefore better functional properties. Inducing and maintaining effective memory is one central characteristic expected from vaccine (natural and elite control). Elite controllers are the model of functional cure, virally suppressed, but not cleared and with the integrity of the immune system maintained relatively intact by the persons own defense without lifelong medications [75].

HIV vaccine delivery strategies

Studies have highlighted differing groups as HIV vaccine targets. Phambili (South Africa) explored participants considered at high risk sexually [80]. The Thailand study recruited HIV-negative male and female volunteers based on the community risk [78]. Mathematical modeling strategies used a round of mass vaccination directed at all individuals aged 15–49 years [59]. Given the development of an extensive school health program in South Africa, together with the highest risk of HIV acquisition being noted among young adult women, opportunistic implementation with the HPV vaccine is being suggested before adolescents become sexually active.

Adolescent participation going forward

The particular susceptibility of adolescents to HIV, STI and HPV is well established [51,84]. Adolescent behaviors predisposing them to HIV transmission and acquisition and the critical biological and socioepidemiological information they hold for vaccine development and eventual roll-out makes their role in HIV vaccine research pivotal. Answers to these sociobehavioral questions cannot be extrapolated from adult data, as evidence shows vastly differing decision-making processes in adolescents compared with adults [85].

Adolescent consent and the custodian for decision-making power over vaccine participation needs consideration as the decision impacts on adolescent relationships and sexual decision making going forward remain unexplored. The major drawback to parental or guardian involvement in consent processes is adolescent reluctance to involve them in trials monitoring sexual behavior and practices. Additionally, child-headed households as a direct consequence of the HIV pandemic remains a real concern in the South African context [53]. South African legislation governing nontherapeutic research in
minors is unclear. Section 71 of the National Health Act allows for research in minors as prescribed (`prescribed' itself is unclear), with either ministerial consent, consent from the parent, guardian or the minor (if capable of understanding). The Minister may refuse consent in circumstances where the objectives could be achieved if conducted in adults; is unlikely to result in significant benefit to minors; poses significant risk to the health of the minor and where the benefit does not significantly outweigh the risk. In its entirety, the document dissuades essential research on the needs of children and serves little ethical purpose [86].

The expedient conduct of well-organized bridging trials will counter the inherent legal and ethical complications of adolescent involvement in clinical trials. Globally, the development of new pharmaceutical products has had to factor geographic variations of efficacy and safety attributed to ethnicity. [87] Pharmaceutical companies are required to provide conclusive evidence of effectiveness and safety elucidated from clinical trials prior to marketing approval for a drug. Regional regulatory authorities often request sponsors to provide region specific clinical data. This extensive duplication of clinical evidence demands valuable development resources and often delays the availability of the new medicine to needy patients in that region.

The International Conference on Harmonization has published a guideline entitled ‘Ethnic Factors in the Acceptability of Foreign Clinical Data’, (International Conference on Harmonization E5 guideline) which provides a general framework for evaluation of the impact of ethnic factors on the efficacy, safety, dosage, and dose regimen. It assesses the acceptability of foreign data for regulatory strategies of minimizing duplication of clinical data and it also describes the requirement of bridging evidence for extrapolation of foreign clinical data to a new region [88].

There are several lessons to be learned from the existing HPV work. Much of the available data is based on bridging studies. For clinical trials going forward, there would be no justification for placebo use when one considers the established efficacy and safety profile of the HPV vaccine. As the epicenter of the global HIV pandemic, South Africa is a convincing location to launch a primary HIV vaccine roll-out and these important considerations have to be borne in mind.

Conclusion
South Africa is at the forefront of the HIV/AIDS pandemic. Coupled with HIV/AIDS, cervical cancer is responsible for significant morbidity and mortality. Public sector vaccine delivery in developing countries is limited by cost and delivery challenges in resource-constrained environments [31]. Discussing vaccine policy has driven efforts to develop national comprehensive cervical cancer strategies that include vaccination, screening, treatment and palliation in areas such as Malaysia, Mexico, Peru, Rwanda, Tanzania and Uganda [6]. Organized public health programs are needed to reach the adolescent population, as well as organization of systems of quality control and vaccine coverage monitoring to ensure long-term follow up for vaccine effectiveness and safety evaluation [6]. HPV vaccine successes and potential HIV vaccine advancements are predicted to encourage even the most underdeveloped countries to scrutinize modalities to reach adolescents and preadolescents with vaccine initiatives [89].

Future perspective
‘Universal’ vaccines eliciting cross-reactive and bNAbs are the Holy Grail to providing protective immunity against HIV [76]. bNAbs have been shown to provide protection at incredibly low doses in animal models suggesting that vaccines capable of stimulating vaccine-induced bNAbs could hypothetically provide sterilizing immunity if present prior to initial HIV infection. Translating these mechanisms to humans would be the ultimate prize. [76] Host controls of bNAbs induction have been described and have pointed the way to new strategies for bNAbs inductions [83].

Several other perspectives of HIV vaccine control have been considered. Immune correlates analyses in the RV144 efficacy trial and in rhesus macaques’ protection models have provided novel directions for vaccine development [83]. There have been attempts to diminish the viral reservoir and eliminate latently infected cells by activation (using IL-7, histone, deacetylase inhibitors and others) in conjunction with the induction of effective cytotoxic responses [75]. While much of these results have been unable to yield the answer that we have been seeking for 30 years, they do provide pieces of a puzzle that stimulate the next advancement in research.

Many low-income countries are eligible for GAVI support for initial and sustainable HPV vaccine introduction. The ‘sustainable’ aspect has been introduced since many country
EXECUTIVE SUMMARY

The link between HIV & HPV
- Invasive cervical cancer has been AIDS defining since 1993.
- Male medical circumcision has been shown to reduce HIV and HPV acquisition.
- Integrating HIV and HPV prevention into a sexual and reproductive health platform will provide a logical continuum of care.

Understanding the global impact of HPV
- Cervical cancer dominates the burden of HPV disease.
- HPV vaccine efficacy is undisputed, but the reduction in disease burden will be unapparent for decades.

HPV epidemiology
- HPV is the most common sexually transmitted infection globally.
- Competing health demands, poverty and poor education challenge primary HPV prevention strategies.

Clinical concepts regarding the natural history of HPV infection
- HPV is opportunistic for sporadic reproduction and transmission and is generally benign unless it persists.

HPV vaccines
- Cervarix® (bivalent; GlaxoSmithKline, UK) and Gardasil® (quadrivalent; Merck & Co, NJ, USA) are safe, immunogenic and prevent infection against oncogenic subtypes (HPV 16 & 18, both) and nononcogenic subtypes (HPV 6 & 11, quadrivalent).
- The vaccines lack therapeutic effect, are expensive and provide limited cross protection.

HPV vaccine delivery strategies
- School-based programs are considered a prime strategy in the developing world to reach adolescents.
- Adolescent immunization requires expansion of health infrastructures to access this largely unreached cohort.

Understanding the global impact of HIV
- Sub-Saharan Africa reports adolescent female (aged 15–24 years) infection rates eight times higher than male counterparts.
- Concerns about enrolling adolescents in HIV studies include testing, stigmatization post-testing and concerns about sexual disinhibition.

HIV epidemiology
- The South African HIV epidemic is generalized, driven by sexual transmission and accounts for 16.2% of global HIV prevalence.
- Steadily increasing HIV prevalence among 15–19 year olds (from 2.4% in 1990s to 14.1% currently) highlights the need for HIV preventative strategies.

Clinical concepts regarding the natural history of HIV infection
- Long-term nonprogressors (1–5% of HIV infected) experience stable disease, lack of decline in CD4+ T cell counts and control of virus replication below 100 HIV RNA copies/ml for extended periods (at least 7–10 years) in absence of antiretroviral therapy.
- Elite controllers (<1% of HIV infected) show control of virus replication <50 RNA copies/ml regardless of time of control.

HIV vaccines
- The genetic diversity of global circulating strains of HIV-1 has hampered vaccine-mediated development.
- Promising data from RV144 showing limited antibody protection and response in human trials has warranted work on an improved regimen for potential licensure in high-risk groups.
EXECUTIVE SUMMARY (CONT.)

HIV vaccine delivery strategies

- HIV vaccine should be administered opportunistically with HPV to adolescents in school programs.

Adolescent participation going forward

- The expedient conduct of well-organized bridging trials will counter the legal and ethical complications of adolescent involvement in HIV clinical trials.

Future perspective

- Low-income countries rely on Global Alliance for Vaccines and Immunisation aid and assistance with infrastructure to develop a sustainable HPV program.
- Vaccine initiatives include targeting the latent reservoir for elimination, enhancing broadly neutralizing antibody development through vaccination and determination of immune correlates of protection.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.


49 Cleary S, McIntyre D. Financing equitable access to antiretroviral treatment in South Africa. *BMC Health Serv. Res.* 10(Suppl. 1), S2 (2010).


REVIEW Moodley & Gray


66 Outlines prevention strategies for targeted key populations.


79 Schiffler T, Sattentau QJ, Dorrell L. Development of prophylactic vaccines against HIV-1. Retrovirology 10(72), 1–16 (2013).


