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Translation of biomedical prevention strategies for HIV: Prospects and pitfalls

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Abstract

Early achievements in biomedical approaches for HIV prevention included physical barriers (condoms), clean injection equipment (both for medical use and for injection drug users), blood and blood product safety, and prevention of mother to child transmission. In recent years, antiretroviral drugs to reduce risk of transmission (when the infected person takes the medicines; treatment as prevention or TasP) or reduce risk of acquisition (when the seronegative person takes them; pre-exposure prophylaxis or PrEP) have proven efficacious. Circumcision of men has also been a major tool relevant for higher prevalence regions such as sub-Saharan Africa. Well-established prevention strategies in the control of sexually transmitted diseases and tuberculosis are highly relevant for HIV (i.e., screening, linkage to care, early treatment, and contact tracing). Unfortunately, only slow progress is being made in some available HIV prevention strategies such as family planning for HIV-infected women who do not want more children and prevention mother-to-child HIV transmission. Current studies seek to integrate strategies into approaches that combine biomedical, behavioral, and structural methods to achieve prevention synergies. This review identifies the major biomedical approaches demonstrated to be efficacious that are now available. We also highlight the need for behavioral risk reduction and adherence as essential components of any biomedical approach.

Keywords

Condoms; PMTCT; TasP; PrEP; PEP; male circumcision; vaccines; complimentary strategies

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Introduction

Condom barriers, blood and needle safety, and the prevention of mother to child transmission of HIV (PMTCT) were the first biomedical strategies to control HIV that did not focus on behavioral risk reduction alone. In the early 1990s, the hopes for an HIV vaccine led to capacity-building in HIV prevention studies and a boost in large scale trials for prevention[1,2]. The use of antiretroviral therapy (ART) in a pregnant woman for prevention of infection to her infant was a prescient test of concept for the use of ART as prevention (TasP). The utility of TasP for preventing sexual transmission was demonstrated by the high efficacy demonstrated by the HIV Prevention Trials Network HPTN 052 protocol. Since 2005, compelling biomedical prevention strategies have been added to the armamentarium for HIV prevention, notably male circumcision and ART for prevention of sexual transmission. Efficacy of combining several of these biomedical techniques into a synergistic (additive or multiplicative) approach remains to be determined.

The history of disease control and prevention is replete with examples of effective tools that are available for use, but are underutilized in the field or the clinic. HIV/AIDS prevention is a prominent case in point, a challenge that the National HIV/AIDS Strategy for HIV in the US seeks to address[3]. Both journalists and scientists have highlighted the disappointing missed opportunities in the HIV epidemic[4-13]. Combination prevention approaches are now available that combine multiple efficacious strategies to block transmission, but all must include behavioral components to avoid risk compensation--the increased risk taking behavior that may accompany prevention approaches that clients perceive to be more effective than they really are[14]. All three early approaches (condoms, clean needles/syringes, and PMTCT) also required structural reform and technical capacity-building to enable widespread dissemination of the interventions. Widespread condom and needle distribution confronted political opposition that inhibited program scale-up in many venues. Even blood safety measures were resisted in the pre-HIV screening era by many blood banking authorities for economic reasons.

In this paper, we will review key biomedical tools for the prevention of HIV transmission (Table 1) and what the prospects and obstacles are for their further utilization in global HIV control. A recurring theme is that we have technologies that can reduce the epidemic, but we have not deployed them widely or consistently[15-20]. Other papers in this *JAIDS* supplement will address behavioral interventions *per se*, so we will restrict our discussion to the issues arising in translation of biomedical tools. We acknowledge the subjective nature of a manuscript such as this one; it is challenging to predict how these tools will have an impact on the global pandemic. However, we believe speculations regarding the scale-up and application of biomedical prevention can be well-informed based on present knowledge of disease control and prevention for HIV/sexually transmitted infections (STI), tuberculosis, and blood-borne infections such as hepatitis B and C.

Antiretroviral treatment (ART) to reduce infectiousness of HIV-infected persons

Sexual transmission

TasP is founded on evidence that persons who are HIV-infected and are on combination antiretroviral therapy (cART) are less likely to transmit the virus sexually than those not on cART. Higher viral load has been associated with higher HIV transmission risk in observational studies[21-30]. Use of cART has been associated with reduced risk for sexual transmission. In 2011, the HIV Prevention Trials Network (HPTN) 052 trial demonstrated definitively the huge benefit of cART use in persons with higher CD4+ T-lymphocyte counts in protecting their sexual partners (hazard ratio of 96% protective efficacy; 95%

confidence interval [95%CI] of 73 to 99%)[31-33]. As this benefit was apparent when cART was offered to persons who would not have qualified for HIV treatment for their own sakes (as per 2009 WHO treatment guidelines), WHO issued new guidelines in 2012 suggesting that where possible, more persons should be treated with cART than had been recommended heretofore[34]. While expanding the eligibility of cART with the aim of TasP represents a significant opportunity to prevent new infection, issues of drug resistance, disinhibition, and logistics complexities must be addressed for this approach to be effective in non-clinical trial conditions[35].

Efforts in high access cities such as San Francisco and Vancouver have made progress in expanding TasP[36-39]. It may be that more than 30 years of work for HIV risk reduction among MSM, with mixed success, has contributed to higher uptake of HIV therapy in these settings[40,41]. In the US as a whole, however, overall program coverage with testing, linkage to care, and therapy remains disappointing[42-46]. Several new controlled community randomized studies are being launching to study combination prevention, including implementation of expanded ART coverage, to assess the impact on community HIV transmission. Four groups intend to launch such studies in 2012 or 2013, some with combinations of TasP, medical male circumcision, and strategic and behavioral intervention innovations. The HPTN 071 POPArt study (Richard Hayes, principal investigator [PI]), the Iringa study in Tanzania (David Celentano, PI), the Botswana study (Max Essex, PI), and the ANRS/Africa Center study (Marie-Louise Newell, PI) all intend to address the ART for prevention question within rigorous community randomized studies. There are a number of smaller studies that also intend to address this question, some of which are in the field for preliminary work.

TasP for injection drug users

While much has been achieved among injection drug users in risk reduction using needle and syringe exchange as well as opiate-agonist based heroin addiction therapy, there are still regions of the world that do not implement these measures. It is plausible that TasP could also be implemented effectively in this population, and such studies are in progress.

Prevention of mother-to-child transmission of HIV (PMTCT)

The earliest test-of-concept for the use of antiretroviral drugs to reduce HIV viral load and infectiousness in one person to protect another was in PMTCT. Evidence from many definitive randomized clinical trials, e.g., the AIDS Clinical Trials Group (ACTG) 076 trial, the HPTN's HIVNET 012 trial confirmed that reducing viral loads with ART could reduce transmission markedly to newborn infants. Subsequently, both cART use in HIV-infected pregnant women during the months of breastfeeding and use of pre-exposure prophylaxis (PrEP) with ART in breastfeeding infants were judged safe and effective in reducing transmission in low income settings where replacement feeding is neither safe nor affordable[47-52].

Despite the proven efficacy of antiretroviral prophylaxis or treatment for PMTCT and the high degree of successful implementation in high and middle income countries[53-55], the proportion of women and infants receiving all stages of PMTCT in resource limited settings has been disappointing[56-64]. Failure to engage mothers and/or infants at any step of prevention continuum (Figure 1) can lead to a failure in preventive efficacy during pregnancy or the post-partum periods. Each of these steps are amenable to clinical and community interventions to improve engagement and coverage. In an effort to document barriers to PMTCT uptake, researchers have often focused on patients, although there is movement towards complementary hospital-based quality improvement approaches[65-70]. Well documented barriers include the lack of PMTCT related care systems capable of

delivering quality service[57,67,71-73], lack of family or community support[65,74,75], stigma[66,67], and concern with confidentiality/treatment at the clinical site[66]. Additional barriers include cost/transportation for travel to the clinic[65], cultural pressure to breastfeed (or concern that not-breastfeeding would 'out' the mother as being HIV positive)[66,76], inadequate alternative food sources for infant feeding[64], inadequate knowledge about HIV transmission[65,74], and a desire to deliver at home or with a traditional birth attendant[65]. These and other barriers to full coverage of PMTCT represent some of the challenges of translating the benefits of biomedical knowledge effectively into real-world settings[56-58,77-82]; other prevention strategies such as TasP and adult circumcision will likely face similar challenges, and will benefit from lessons learned from PMTCT field experience in low-resource settings.

Systems strengthening for implementation of PMTCT and TasP

Widespread health system deficiencies have been identified in a number of low income countries that lead to a low uptake and adherence to ARV prophylaxis[56,61,83] and EID[84]. Although socioeconomic factors are often cited as drivers of poor access to PMTCT or EID[85-88], there is increasing attention to the role that strengthening health systems may play in improving access and other program outcomes[89-91], and efforts are underway to strength health systems to improve PMTCT-related care[92,93]. In one study at two district hospitals in rural Mozambique, health systems barriers preventing access to EID were addressed using a conceptual framework for quality improvement adapted from Langley et al[92]. The process of maternal post-partum care for HIV-infected mothers was analyzed at each hospital; a two phase intervention was designed with the help of nursing staff and patients and evaluated using a before/after intervention study design[69,70]. Hospital staff were introduced to the Langley model for quality improvement and given the opportunity to participate in the study by describing the process of care, identifying modifiable health system barriers, and designing an intervention aimed at impacting infant retention in EID. The standard process of referral to the EID clinic during maternity discharge was identified as a target for improvement and an intervention was designed that enhanced referral by more tightly linking maternity and EID services through direct accompaniment and by providing privacy for women during counseling. After 2 cycles of intervention, the proportion of mother/infant pairs that succeeded in accessing EID within 3 months of the child's life improved by 55%. This is but one example highlighting the potential benefit of practical, site based innovations to improve retention for HIV prevention from mother to child[90,93]. Scaling up of quality improvement based strategies is an essential approach to strengthen health systems and make the best use of available resources in developing countries.

Complementary Strategies to PMTCT

Implementing an intervention designed to create and sustain behavior change is another alternative to increasing access to biomedical interventions, but this may be a gradual process of education and culture change[94]. Attempting to change maternal birthing practices and early childrearing behavior can be especially challenging, as target behavior may conflict with culturally accepted practices and beliefs. Traditionally, interventions to improve uptake have been targeted at pregnant women[95-97]. Recently, the importance support from husbands in ensuring uptake of PMTCT has been addressed through the engagement men in antenatal HIV counseling[65,98] and changes to hospital or clinical systems[58,59,68,93,99].

Many HIV-infected women who would like to plan their family size do not have access to contraception; it has been estimated that filling the unmet need for contraception among all the HIV-infected women who need it would result in a huge decline in mother-to-child transmissions[100-121]. While this is not TasP, it is another PMTCT intervention that depends

on capacity building and broadening of the HIV prevention mandate to include other primary health care needs in afflicted communities. Concerns that hormonal contraception use in seronegative women may result in higher risk of acquisition do not apply in the case of seropositive women[122,123]. Furthermore, there are alternative approaches to hormonal use that are being underutilized, including the intrauterine device[124-127].

Antiretroviral prophylaxis to reduce susceptibility of HIV-uninfected persons

Pre-exposure prophylaxis (PrEP)

At a May 10, 2012 meeting, the U.S. Food and Drug Administration's Antiviral Drugs Advisory Committee recommended approval of a drug labeling “efficacy supplement” for the use of Truvada® tablets (each tablet has 200 mg of emtricitabine [FTC] and 300 mg of tenofovir disoproxil fumarate [TDF], made by Gilead Sciences, Inc.) for PrEP, namely oral tablet use for prevention of HIV transmission in HIV-uninfected persons. Oral PrEP has been consistently effective in successive trials in men, ranging from 44-68% efficacy in clinical trials such as iPrEx, Partners PrEP, and TDF-2[128-132]. In women, the Partners PrEP and TDF-2 studies suggested oral PrEP efficacy, but the FEMPrEP[133] and VOICE[134,135] trials did not, though the FTC/TDF oral PrEP arm of the VOICE trial continues as of this writing (June 2012). Similarly, use of a topical 1% tenofovir microbicide intravaginally worked to protect against HIV in women in the CAPRISA 004 trial[136], but did not work in the VOICE trial[137,138]. Hence, the evidence is more consistent that oral PrEP works well in men, but is less consistent for oral and for topical PrEP in women (Table 1). Rectal microbicides (also topical PrEP, but designed for anal sex protection) are theoretically useful for women and men practicing anal sex, but they have not yet been tested in Phase 3 clinical efficacy trials. Topical PrEP remains an area of intense current investigation[139-144]. Opinions differ as to the likely utility of PrEP as a substantial public health tool for HIV prevention, though a female-controlled product could be a valuable additional to women's options[145-148].

Post-exposure prophylaxis (PEP)

Occupational exposure to needle stick injuries, surgical instruments, or other substantial medical injuries within the context of caring for an HIV-infected person can expose health care workers (or even sanitation workers) to HIV[149-151]. Post-exposure prophylaxis with cART is now standard practice for many high risk exposures (with higher volume in persons who are not viral load suppressed, to give one example) and is an option for prophylaxis even in lower risk exposures[152,153]. Again, implementation issues loom large: successful PEP requires reducing the risk of the needle exposure to begin with, prompt reporting of needle stick injuries, and successful adherence of exposed staff to the cART PEP regimen[154].

PEP is also an alternative for inadvertent sexual exposure, as with condom breakage or non-use, or with rape. Randomized clinical trial evidence is lacking for both occupational and non-occupational PEP, but epidemiology suggest cART to be possibly effective for reducing transmission risk[155,156]. Again, the translation of PEP efficacy to population effectiveness depends on working systems of surveillance, availability of expertise and cART, willingness of the exposed person to uptake the PEP intervention, and their success in adherence to PEP. The HPTN 040 study demonstrated in an RCT that PEP given to infants born to mothers who had not received ART worked to prevent infant infection[157-160]. Intrapartum transmission occurred in 3.2% (47) of infants studied. Transmission rates were significantly lower in the ZDV + NVP arm 2.2% (11) (95% CI: 1.2 to 4.0, p = 0.045 and the ZDV+NFV +3TC 2.5% (12) (95% CI: 1.4 to 4.3%, p = 0.045) compared to the ZDV arm[157-159].

Medical male circumcision to reduce susceptibility

Ecological and epidemiological evidence has suggested that infant or later circumcision might reduce HIV transmission risk[161-165]. Voluntary medical male circumcision in adults was tested in three RCTs in sub-Saharan Africa whose results were remarkably consistent[166-168]. Hence, when the cheaper, simpler, and safer infant circumcision had not been performed previously, adult male circumcision is deemed advisable in high HIV prevalence settings. There are obstacles to uptake: cultural acceptability, fear of pain and/or surgical mistakes, and poor understanding about the risks and benefits of circumcision[169-183]. The decision to circumcise or not are often based more on social acceptability than medical evidence. In sub-Saharan Africa, rites of passage for men often include circumcision (traditionally conducted outside of a clinical setting) presenting an opportunity for health workers to incorporate safe surgical practices into traditional rituals. Education campaigns and improved access to safe surgical services has led to increased uptake among communities where circumcision was uncommon[184,185]. Western countries are experiencing the opposite trend. The belief that male circumcision is akin to genital mutilation is becoming more widespread. Some researchers and laypeople argue that it leads to long-term psychological trauma in the male infant, impacting everything from mother-son bonding to future sexual relationships, although there is no scientific evidence to support this belief.

Male circumcision of either HIV-infected men or HIV-uninfected men who later seroconvert may reduce their infectiousness to others through reduction of sexually transmitted infections (such as the very common human papillomavirus) among other potential mechanisms[186-199]. However, if men have sex before their wounds are healed, after surgery, risk could rise as observed in Uganda[200]. Also, risk compensation is a concern if men increase high risk behavior because they have been circumcised and no longer perceive personal risk[201,202]. If proper technical procedures, risk reduction counseling, and community consultations are adhered to, male circumcision is a theoretically powerful tool, especially when incorporated into a combination prevention strategy designed to reduce risk through behavioral modification and biological interventions[164,203-207].

Evidence that circumcision will prevent HIV acquisition or transmission among men who have sex with men (MSM) is not consistent and is less likely to be as strong in its association as with heterosexual transmission[195,208-211]. For example, being circumcised may not help much if one is the receptive partner in MSM sexual relations. Infant circumcision is cheaper, easier, and less risky than adult circumcision. An excellent long-term investment is seeking universal male infant circumcision in high prevalence regions to nurture a new generation of lower risk men[169,212-219].

HIV vaccines to reduce susceptibility (preventive vaccines)

In a huge RCT in Thailand (n=16,402), a 4-dose priming live vector canarypox vaccine (ALVAC-HIV® [vCP1521]) vaccine followed by 2-dose gp120 subunit bivalent (AIDSVAX B/E®) booster regimen proved somewhat efficacious in preventing HIV infection[220]. The modified intention-to-treat analysis excluded seven participants who had acute HIV-1 infection at baseline unbeknownst to the investigators, finding a vaccine efficacy of 31% (95% CI: 1 to 52%)[221]. The vaccine regimen did not reduce the viral set-point in participants who seroconverted despite being in the vaccine group. Despite this success, neither product is being carried forward into production nor is the trial being confirmed to propose licensure. This illustrates the global economic dynamics of vaccine development; only a more efficacious product is likely to inspire the private sector to license and market the vaccine.

Successful vaccine development is no longer just a theoretical possibility; having succeeded in primate animal models and now in a human RCT, investigators will not rest until a viable and more efficacious product is developed[222,223]. This suggests a host of challenges from which we can learn from other vaccine experiences. HIV is an STI, so suboptimal coverage with hepatitis B vaccine and human papillomavirus vaccine (the only licensed STI vaccines) in adolescents and adults suggests that HIV vaccine deployment would run into the same problems[224-229]. We have no good global vaccine infrastructures or routine health care engagement for adult vaccination. There is some reticence to agree to STI vaccines given stigma, including among parents for their children[230]. Continued challenges in global vaccine coverage, even for childhood vaccines, are to be expected to be relevant for HIV vaccines, once available[231]. This includes anti-vaccine forces claiming the lack of cost-benefit evidence for vaccines, spurious toxicities attributed falsely to vaccines, and arguments about immunological overload that have no evidence to support them[232,233].

One of the principal objections voiced to STI vaccines is that of disinhibition, or risk compensation, the possibility that if someone is protected against an STI, then they might be more likely to engage in risky behavior. In the early hepatitis B virus (HBV) vaccine RCTs, there was a rise in HBV incidence after the first dose of HBV vaccine, attributed to disinhibition among men who had sex with men (MSM) who were in the trial[234,235]. Hence, this potential risk must be taken seriously and studied alongside prevention technology benefits.

HIV vaccines to reduce transmissibility (therapeutic vaccines)

An effective vaccine given to HIV-infected persons could theoretically reduce the viral load in the infected person by enhancing or complementing natural, imperfect immune responses. Animal models have suggested feasibility of such approaches in idealized experiments, but no human data have been convinced to suggest that any tested products have been effective[236].

Treatment of co-infections to reduce HIV viral load and transmission risk

Co-infection with such infectious agents as *Mycobacterium tuberculosis*, helminthes, herpesviruses, and syphilis can cause immune activation and upmodulate HIV expression[27,237-239]. Coinfection with Schistosoma haematobium is associated with increased HIV risk, as was seen previously for STIs, perhaps related to the disruption of integumentary integrity and/or local inflammation[240-243]. Rhesus macaques infected with *Schistosoma mansoni* more susceptible to HIV and shed more HIV once infected[244-247]. Treatment or suppression of the co-infections can reduce plasma and presumably genital viral load, as suggested in genital herpesvirus suppression studies[248-255]. Thus, excellent primary care for HIV-infected persons that involves co-infection treatment or suppression could reduce transmissibility of HIV by reducing HIV viral load and transmissibility.

Clean needles and syringes for injection

Despite global reductions in HIV infection, substance use specifically injection drug use (IDU) continues to be a significant driver of the epidemic[256]. IDU has been estimated to be responsible for about 9% (3 million) of the 34 million persons of persons living with HIV globally, including about 17% of prevalent HIV cases in the US[257,258]. The WHO estimates that one out of ten new HIV infections globally is attributed to IDU, and CDC suggests IDU to be associated with 9% of new HIV infections in the US[258,259]. Eastern Europe and Central Asia continue to incur high rates due to IDU; the numbers infected with HIV in these regions have tripled over the past decade[259-261]. To stem the impending surge in new cases in regions not yet saturated and/or effectively implemented control measures, multiple

prevention strategies have been implemented with various degrees of success. Harm reduction efforts such as opioid substitution therapy (OST) and needle and syringe programs (NSPs) have shown to be effective at reducing HIV in IDUs[9,262-264]. Needle exchange was one of the first methods used in the public health arsenal to control the epidemic. NSPs not only provide sterile needles and equipment; they provide an avenue for HIV, STI, substance abuse and mental health care and treatment to a marginalized risk group. Since the mid-1980's NSPs have emerged around the world with great success, most notably in Canada, Western Europe, and Australia[260]. However coverage has been stymied by controversy, government imposed regulations, and lack of available resources. Out of the 151 countries where IDU is prevalent, only 82 countries have implemented NSPs and OST is provided in 71; however coverage is variable across programs and regions[260]. LMIC countries have been unable to meet the WHO distribution guidelines of 200 syringes per IDU per year[265]. In the US, NSP support is wrought by politics and regulation. In 2009, the ban on using US federal funds for NSPs was lifted by the Executive Branch of government only to be reinstated by the Congress in the 2012 federal budget[266,267].

The peril of extensive nosocomial HIV transmission has been demonstrated in major outbreaks in Russia, Libya, Romania, and other countries [42, 43]. Medical injections were implicated in each of these outbreaks. The importance attributed to unsafe medical injections in the transmission of HIV in sub-Saharan Africa has been minimized by the enormous attentions given to sexually transmitted HIV [44]. The perception that unsafe medical injections are rare in sub-Saharan Africa rests on the assurance in health workers' training and supervision, and compliance with existing safety guidelines. In 2008, studies in South Africa highlighted cases of HIV transmission in children two to nine years' old receiving immunizations in public health facilities; interviews with health care workers reported reusing syringes [45]. Working under rationing pressures and without an accurate estimate for the HIV transmission risk in an individual injection may predispose health workers to view single-use protocols for injection safety as unacceptably wasteful [46]. Programs to improve provider practices; reduce community demand for injections; support the procurement of appropriate injection commodities to eliminate re-use of syringes and needles and improve safety are still needed in these settings.

Transfusion

In higher income countries, public concern has obliged blood collection agencies and policy makers to continue to search for more sensitive HIV screening tests, despite a dramatic decrease in the transmission of HIV infection through blood transfusions[268-271]. The availability of HIV-1 p24 antigenic testing and state-of-the art genomic amplification techniques, while expensive, allow for the identification of the vast majority of window-phase donations[270,272]. The impact of other less expensive strategies on HIV transmission risk reduction, such as donor deferral and the non-use of donations from higher risk sub-populations has been highlighted in low income countries[273-277]. Unfortunately, these cost-effective strategies are not being applied consistently[273,274,278-280]. While progress towards improving safe and adequate supplies of blood is being made [278], continued government commitment is critical for ensuring quality, safety, and adequacy of the blood supply, particularly in lower income nations where challenges in capacity, logistics, and infrastructure are common.

Physical barriers to virus-cell contact

Consistent and correct condom use is estimated to provide an 80% reduction in HIV seroconversion[281]. Male condoms are inexpensive, widely-accessible, have few side effects, and (among many populations) are a culturally acceptable HIV prevention intervention. The

number of condoms used worldwide is increasing, possibly due to increased social marketing campaigns to increase social acceptability in casual and committed relationships[282]. While condoms reduce the risk of HIV transmission, evidence suggests they are used inconsistently[282-284]. Negotiating condom use can be difficult for women as the decision to use a condom often rests with her partner.

Female condoms were designed to provide women with more control over their sexual safety, but uptake has been low[285,286]. Women needed considerable training and motivation to use the first generation products successfully[287-290]. New generation products are better designed and may be more appealing; studies are in progress[291]. Among couples where both partners actively participate in the decision-making process, condoms may be eschewed for other reasons: cost, feel, availability, desire for pregnancy, the belief that they are unnecessary in a 'serious' relationship, or religious beliefs may sway partners to have unprotected sex[292-294].

Conclusions

The finding of an efficacious intervention in one venue does not guarantee success in a different cultural context. A prime example is the control of the HIV epidemic among IDUs in Australia vs. the continuing spread in Russia; lack of political support for universal NSP and a ban on OST in Russia fuel their IDU-related HIV epidemic[260,295,296]. A second example is the success in the 1990s with HIV prevention in Uganda, contrasted to that seen in its neighboring nations[297-300]. Standardized approaches for adapting interventions to new contexts have been developed, including RE-AIM[301,302] and ADAPT-ITT[94,303], but adaption of behavioral interventions is time-consuming and fraught with potential challenges. The tailoring a given epidemic response to local drivers of transmission is needed for both effectiveness and efficiency. Combination prevention approaches are most promising, but they require substantial success in achieving coverage metrics beyond those achieved in most global programs[304-306]. The good news is that the myriad of biomedical intervention strategies now demonstrated to be effective in reducing HIV transmission can be combined to make major inroads into the global pandemic[307,308]. Even as we research new approaches, the scientific community shares an urgent obligation to communicate current opportunities to policymakers, funders, and communities to motivate HIV control and prevention[309].

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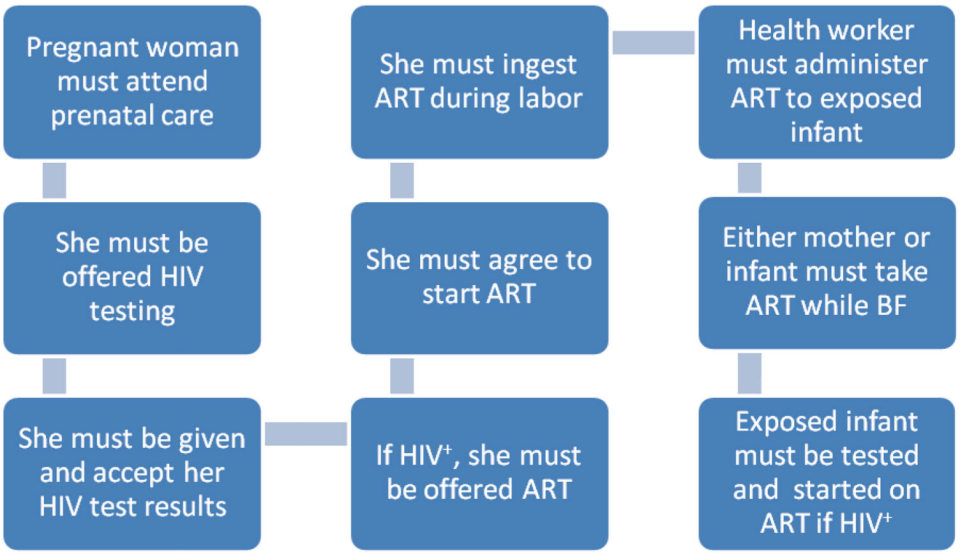

Figure 1.
The prevention of mother-to-child transmission of HIV cascade: steps required to realize the full benefit of testing and linkage to antiretroviral-based antenatal and post-partum care. ART=antiretroviral therapy; dx=diagnosis; BF=breastfeeding

Table 1

Biomedical approaches to HIV prevention and strength of evidence RCT=Randomized clinical trial; EPID=Epidemiologic evidence; ECOL=Ecological associations; OR=Outcomes research; PrEP=pre-exposure prophylaxis; PEP=post-exposure prophylaxis; STI=sexually transmitted infections

Biomedical HIV prevention strategy	**Highest Level of Evidence**
Antiretroviral treatment to reduce infectiousness of HIV-infected persons	
--in sexual relations	RCT, >95% efficacy
--from mothers to infants	RCT, >98% efficacy
--among injection drug users	EPID
Antiretroviral prophylaxis to reduce susceptibility of vulnerable HIV-uninfected persons	
--oral PrEP in men	RCT, 44-68% efficacy
--oral PrEP in women	RCT (inconsistent)
--rectal microbicides (topical PrEP) for men/women	Animal models
--vaginal microbicides (topical PrEP) for women	RCT (inconsistent)
--PEP for needle stick injuries	EPID
--PEP for sexual exposure, including rape	EPID
--PEP for infants born to mothers not receiving ART	RCT
Medical male circumcision to reduce susceptibility	
--Voluntary medical male circumcision in adults	RCT
--Infant circumcision	EPID and ECOL
Medical male circumcision to reduce infectiousness	
--i.e., reducing HIV transmission risk from an HIV+ man	RCT, 38-68% efficacy
HIV vaccines to reduce susceptibility (preventive vaccines)	
-- ALVAC-HIV® [vCP1521] prime plus AIDSVAX B/E® boost*	RCT
--Other vaccines	Animal models
HIV vaccines to reduce transmissibility (therapeutic vaccines)	
--i.e., vaccine given to HIV+ person to reduce viral load	Animal models
Treatment of co-infections to reduce HIV viral load and presumed transmission risk	
--e.g., tuberculosis, helminthes, STI	Animal models, EPID
Clean needles and syringes for injection	
--Needle/syringe exchange programs	EPID, OR
--Medical injections	EPID, OR
State-of-the-art blood banking	
-- Sensitive HIV tests to screening blood/blood products	EPID, OR
--Non-use of donations from higher risk sub-populations	EPID, OR
*Physical barriers to virus-cell contact***	
Male condoms	EPID, OR
Female condoms	EPID, OR (inconsistent)
Prevention of unwanted pregnancy to reduce pediatric HIV infections	
Contraception: e.g., hormonal, intrauterine device, barrier	EPID

* 4 injected priming doses of recombinant canarypox vector vaccine (ALVAC-HIV® [vCP1521]) followed by 2 injected booster doses with recombinant glycoprotein 120 subunit (AIDSVAX B/E®); details of vaccines are in the online manuscript supplement: http://www.nejm.org/doi/suppl/10.1056/NEJMoa0908492/suppl_file/nejm_rerks-ngarm_2209sa1.pdf, accessed May 12, 2012

** Not listed are other techniques that are theoretically beneficial, but have not proven efficacious, e.g., vaginal diaphragm, or have not been tested, e.g., cervical cap

NOTE: Beyond the scope of this table are **behavioral approaches** towards abstinence, delayed sexual debut, risk reduction among seropositive persons, partner fidelity, including reducing the number of partners, partner selection, including serosorting for persons to have sex only with others with the same serostatus, exclusive breastfeeding for seropositive mothers and uninfected infants, community mobilization for stigma reduction and changes in behavioral and social norms, and altered health care worker practices such as avoiding unnecessary blood/blood product use. Similarly, **structural changes** are beyond our table's scope, including enforced 100% condom use policies in brothels, behavioral economic approaches such as contingency case transfers to maintain desired behaviors, and adherence to prescribed risk reduction or therapeutic strategies. The authors wish to emphasize the importance of these approaches, but we do not categorize them as biomedical interventions, the topic of this paper.