

## Review article

# Biomedical prevention: what is the current status?

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Biomedical HIV prevention strategies for primary or secondary prevention of HIV transmission can be seen as an adjunct to behavioral prevention approaches. These interventions include vaccination, female controlled vaginal microbicides, male circumcision, treatment of sexually transmitted infections that cause genital ulceration, Pre-Exposure Prophylaxis (PREP) and Post-Exposure Prophylaxis (PEP). This article reviews results from recent randomized controlled trials of novel biomedical prevention approaches and discusses interpretation of the results. The only intervention consistently demonstrating reductions in HIV transmission was adult male circumcision in Sub-Saharan Africa. Results of PREP trials will be available in the next several years.

**Keywords:** Biomedical prevention, HIV

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Biomedical HIV prevention strategies have become a major public health initiative to halt the continuing epidemic that is underway worldwide [1]. Going hand in hand with behavioral prevention approaches to behavior change, the biomedical strategies consist of a wide range of initiatives [2] for the primary or secondary prevention of HIV transmission. These initiatives include the search for a prophylactic vaccine that will provide sterilizing immunity (which is considered to be the primary outcome desired), the use of female controlled vaginal microbicides, the provision of proven antiretroviral medications for HIV prevention (through Pre-Exposure Prophylaxis [PREP] as a primary prevention effort among high-risk but HIV uninfected persons, by treating the HIV infected partner of HIV discordant couples, a secondary prevention approach, or via Post-Exposure Prophylaxis [PEP] once an HIV uninfected person is exposed to HIV), and alternative barrier methods (such as the female diaphragm and male and female condoms). Of note is the series of recent consistent findings that male circumcision might prove to be a potent prevention strategy in Sub-Saharan Africa [3-5].

Several recent reports of randomized controlled trials (RCTs) of novel HIV prevention strategies and technologies have been disappointing. There was a lack of significant findings from many large, well-designed trials. With the exception of the three RCTs of adult male circumcision in Sub-Saharan Africa [3-5], recent trials of biomedical and behavioral prevention interventions have either been under-powered [6], have shown no efficacy for HIV prevention (see table 1), or, more alarmingly, have demonstrated increased rates of HIV acquisition in treatment arms [7, 8]. These disappointments, which are exacerbated by the large expenses that are typically associated with such trials, have led to growing pessimism about the global HIV prevention effort and increased concerns in both the scientific and lay populations about implications for novel interventions currently being tested such as PrEP.

## Recent RCTs of novel HIV prevention approaches

Shifting incidence estimates have coincided with the dissemination of a series of disappointing results from HIV incidence endpoint RCTs of both biomedical and behavioral interventions. Biomedical interventions for HIV prevention including the STEP trial [7], the Carraguard trial [8], the MIRA trial [9], and the Partners in Prevention trial [10] (see **Table 1**) showed no efficacy in reducing HIV seroincidence and in one

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instance, the STEP trial, vaccine recipients with elevated Ad5 titers actually had significantly greater HIV incidence than participants randomized to placebo. The only biomedical intervention tested by an RCT to have significantly demonstrated a consistent benefit has been male circumcision [3-5]. However, HIV acquisition was elevated when men resumed sexual activity before the recommended healing interval and for the partners of HIV infected men, circumcision has not shown consistent protective effects [11].

Microbicides, topical agents to protect against the sexual transmission of HIV [12], were originally targeted for vaginal use, but more recently the need for effective microbicides for anal use has been recognized. Surfactant and polyanionic microbicide candidates have been shown in a series of Phase 1, 2 and 3 trials to be largely lacking in efficacy and in some cases, in safety (e.g., in the cellulose sulfate trials). Recent results of PRO 2000 (naphthalene sulfonate) have generated some enthusiasm in the field, although the results are of borderline statistical significance in preventing HIV transmission [13]. Promising new microbicides lack spermicidal and anti-microbial effects other than HIV. These include reverse transcriptase inhibitors and viral entry inhibitors that are in development or early phase studies. Whether they will be effective singly or in combination is not yet known.

STIs that cause genital lesions are hypothesized to increase the likelihood of HIV acquisition and transmission. A study in Mwanza District of Tanzania in the early 1990s investigated the influence of intensive syndromic management of bacterial sexually transmitted infections on HIV incidence. A 40% reduction in HIV acquisition was noted in the intervention communities as compared to control communities [14]. However, this success was closely followed by several other trials that failed to find such an outcome [15]. Combined study results from 19 longitudinal investigations showed that HSV-2 infection was associated with a risk ratio of 2.7 (and higher for women) [16]. However, two trials of HSV-2 suppressive therapy using the drug acyclovir failed to reduce HIV acquisition in international settings [20, 27]. Thus, promising epidemiologic data were not supported by randomized clinical trial results.

Three major trials of adult male circumcision have been reported in Sub-Saharan African countries with generalized HIV epidemics, and showed similar and strong effects on reducing HIV incidence, on the average, by 52% [3-5]. However, recent data on STI rates among circumcised and non-circumcised men in New Zealand found no effect [18], and an Australian study found that circumcision was not associated with prevalent or incident herpes simplex virus type 1, self-reported genital warts, incident urethral gonorrhea, or Chlamydia, but was associated with a reduced hazard

**Table 1.** Recent biomedical HIV prevention trial results.

| Project                | Intervention                   | Location                                    | Study Participants   | Findings   |
|------------------------|--------------------------------|---|--|--|
| STEP                   | Prophylactic HIV vaccine       | U.S. South Africa, Australia and Caribbean. | 3000 HIV- women, MSM & Caribbean heterosexual men w/ sexual &/or drug risk | Vaccine associated with higher HIV incidence than placebo at elevated Ad5 titres |
| RV144                  | Prophylactic HIV vaccine       | Thailand                                    | 16,395 HIV- low risk Thai citizens   | Vaccine efficacy was 31.2% (95% CI: 1.1, 51.2), p=0.04                           |
| Carraguard             | Vaginal Microbicide            | South Africa                                | 6202 HIV- women aged 16+   | No HIV prevention efficacy   |
| MDP 301                | Vaginal Microbicide (PRO 2000) | 6 sites in 4 African countries              | 9385 HIV- women  | No HIV prevention efficacy   |
| MIRA                   | Diaphragm                      | Zimbabwe, South Africa                      | 5,045 HIV- women   | No HIV prevention efficacy   |
| Partners in Prevention | Aciclovir                      | Africa, Peru and U.S.                       | 3172 HIV-/HSV-2+ women and MSM   | No HIV prevention efficacy   |
| Male circumcision      | Adult circumcision             | South Africa, Kenya, Uganda                 | A total of 10,872 HIV- heterosexual men in three trials.                   | 52% decrease in HIV incidence among circumcised                                  |

of incident syphilis among HIV-negative homosexual men [29]. Whether these results can be generalized to other MSM internationally is not known, but if these results were replicated, circumcision is unlikely to have major public health impacts in reducing STI rates among MSM.

Post-exposure prophylaxis (generally limited to non-occupational exposures) [20] is being evaluated in a number of trials based on the successful animal model of tenofovir (TDF) administration following simian immunodeficiency virus infection when given within 24 hours of exposure and then provided for 28 days. The chief combination treatment includes the use of AZT or tenofovir (TDF) with 3TC along with a protease inhibitor, a very costly regimen that is unlikely to be available in many developing country setting. Pre-exposure prophylaxis is the use of antiretrovirals before exposure to HIV. A number of trials are due to be released in the next several years primarily based on TDF alone or in combination with emtricitabine (FTC).

The report of the Thai HIV prophylactic vaccine trial (RV144) that was unveiled at the Paris International Vaccine meeting on October 20, showed a modest protective effect of the vaccine in a massive study. The modified Intent to Treat analysis demonstrated a suggestive effect ( $p=0.04$ ), although the biological mechanism remains questionable. However, these findings may lead to further investment of vaccine products, giving some hope that immunity may be uncovered in the near future.

RCTs of behavioral interventions, even those that have used behavioral measures in conjunction with or instead of HIV or STI incidence as an endpoint, have had similar results. Five major recent trials including the EXPLORE trial [21], the HIV Prevention Trials Network (HPTN) 037 [6], the Thai Methamphetamine Trial [22], the NIMH Collaborative HIV/STD Prevention Trial [23], and the MEMA kwa Vijana Trial [11] found no efficacy in favor of the experimental group as compared to control groups or communities.

There is some evidence, however, to suggest that pessimism about HIV prevention efforts may be unwarranted. HIV prevention interventions, including community and patient education and outreach, HIV voluntary counseling and testing (VCT), condom promotion and distribution, sexually transmitted infection (STI) treatment and care, and targeted prevention strategies for those most at risk, have

generated significant declines in HIV related risk behaviors and HIV prevalence and incidence in both generalized and concentrated epidemics [24-28]. Rather than a series of high profile RCT failures, HIV prevention may be more appropriately viewed as a widespread and generally successful series of low-profile, behaviorally based community efforts, which have shown success in the control of HIV [29].

Undeniably, there are particular regions in the world, such as southern Sub-Saharan Africa, and specific populations, such as some cohorts of men who have sex with men (MSM), where prevention interventions have faltered and incidence rates remain high. It is within these environments and groups that HIV prevention RCTs, which are driven by statistical power considerations should be mounted. The many disappointments of recent RCTs of HIV prevention strategies warrant an exploration of our prevention strategies.

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