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Review Article

Combating HIV/AIDS: Biomedical Approaches Towards Prevention

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ABSTRACT

For over three decades, HIV/AIDS has had a deleterious impact on public health the world over. There is still no cure for the disease although preventive strategies have evolved over the years to reduce its impact. In addition to behavioural change approaches, biomedical interventions have played a major part in reduction of HIV transmission and subsequently the burden associated with the HIV/AIDS disease. Early biomedical approaches include physical barriers such as condoms, use of clean injection equipment for intravenous drug users, blood and blood product screening. More recently, medical male circumcision and use of anti-retroviral drugs for prevention have been introduced. While these interventions have had a fundamental impact in reducing HIV incidence, the burden in many populations remains. Therefore, there is need to develop new biomedical methods to augment existing efforts. Future biomedical approaches may for instance include use of compounds that modulate the body's immune system, such as acetylsalicylic acid, to cause resistance to HIV infection. Such approaches could be added to the HIV prevention toolkit.

Keywords: *HIV/AIDS, biomedical, prevention, immune quiescence*

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INTRODUCTION

The human immunodeficiency virus has been a great threat to public health since its discovery in early 1980s (Barre-Sinoussi *et al.*, 1983). Approximately 36.7 million people worldwide were living with HIV/AIDS by the end of 2016 (UNAIDS, 2016). Although great strides have been made towards combating this disease, the number of new HIV infections has remained high especially in the last 10 years. In 2016 alone, 1.8 million new infections were recorded (UNAIDS, 2016). HIV/AIDS thus continues to be a huge health, social and economic burden. The advent of antiretroviral (ARV) therapy changed the course of HIV treatment but an efficacious vaccine or biomedical cure is yet to be found. Prevention methods remain the best option to bring to a halt HIV transmission. Both primary (to reduce incidence) and secondary (to reduce disease prevalence and severity) HIV prevention programs employ various strategies. Behavioural strategies include education on sex and stigma reduction, psycho-social support programs. Structural programs such as legislation to reduce gender inequalities, stigma and discrimination, economic and community empowerment especially for women (UNAIDS, 2010) are also incorporated in HIV prevention programs.

Biomedical methods encompass clinical, medical and epidemiological approaches. Earlier biomedical methods included physical barrier methods such as condoms; and harm reduction methods encompassing injection and needle exchanges, opioid substitution therapy, blood and blood product screening. More recently voluntary medical male circumcision, use of ARVs in treatment as prevention (TasP), PMTCT, as well as microbicides and vaccines have been developed. Notwithstanding, the need to enhance and/or develop new efficacious biomedical preventative methods remains a public health priority. Newer frontiers for prevention could include strategies that modulate the immune system of the body to resist HIV infection.

PHYSICAL BARRIER APPROACH

Condoms, both male and female, provide a physical barrier to prevent HIV transmission. Condoms are included as part of the ABC (abstinence, being-faithful and condom use) initiative employed from early 1980s towards HIV and sexually transmitted infections (STIs) prevention. Correct and consistent condom use has been shown to decrease hetero-sexual transmission of HIV-1 (Sánchez *et al.*, 2003) and risk of *Gonorrhoea* and *Chlamydia* infections (Cohen, 2003). Effectiveness of condom use for prevention of HIV transmission is dependent on correct and consistent use. Overall, among heterosexual persons, condoms have been reported to have 64%-94% effectiveness to reduce HIV transmission rates. Among men who have sex with men (MSM) effectiveness has been reported at 70% (Smith *et al.*, 2015). A global modelling analysis in 2014 estimated that since the beginning of the epidemic, about 50 million new HIV infections were averted by use of condoms. However in spite of this, condom use does not take into consideration persons who do not acquire HIV hetero-sexually such as intravenous drug users (IDUs) (Murphy *et al.*, 2006) or those unable to negotiate for condom use with their sexual partners.

HARM REDUCTION METHODS

The notion of reducing harm and subsequently HIV was also introduced in early 1980s. IDUs are orally administered with replacement drugs such as methadone or buprenorphine in opioid substitution therapy programs. This is done in clinical settings to wean IDUs off illicit drugs. Aside from helping to curb illicit drug use, such measures help reduce HIV risk behaviour and improve adherence to ARV treatment (UNAIDS, 2010). Clean needle and syringe exchange programmes provide IDUs with access to sterile needles and syringes as a harm reduction measure, thus reduce transmission of HIV and/or other viral blood borne illnesses caused by sharing injection equipment (UNAIDS, 2010). In hospital settings, screening of blood and blood products before transfusion is useful to prevent blood-borne exposure to HIV. Overall, harm reduction is a combination of actions including HIV education, HIV counselling and testing, that aim to limit the exposure to HIV infection.

VOLUNTARY MEDICAL MALE CIRCUMCISION (VMMC)

The penile foreskin predisposes men to HIV acquisition as it contains many target cells in its squamous lining, including Langerhans' cells, memory CD4+ T and dendritic cells (McCoombe and Short, 2006). Additionally, the foreskin is at risk of small tears during sexual intercourse providing a potential route of entry for STIs in uncircumcised men (Gray *et al.*, 2017). Circumcision, surgical removal of the foreskin, has been demonstrated to confer approximately 60% protection against HIV acquisition in men (Gray *et al.*, 2017; Bailey *et al.*, 2007; Auvert *et al.*, 2005). In light of this, the World Health Organisation (WHO) and the Joint United Nations Program on HIV/AIDS (UNAIDS) recommended addition of voluntary medical male circumcision (VMMC) to HIV prevention programs (WHO, 2007) particularly in countries with high HIV burden. Though highly effective VMMC is not fool proof; it is only one aspect in HIV prevention. It should be combined with the promotion of condom use, safe sexual practices, STI management, HIV testing and counselling (WHO, 2012); and in some cases measures such as treatment as prevention and microbicide use.

TREATMENT AS PREVENTION (TasP)

Since the 1990s, antiretroviral therapy (ART) has been effective to manage HIV infection. ART can slow down disease progression (WHO, 2015; Kitahata *et al.*, 2009) and decrease HIV-1 viral load (Montaner *et al.*, 2011) in blood (Gulick *et al.*, 1997), semen (Gupta *et al.*, 1997), rectal fluid (Zuckerman *et al.*, 2004, 2007) and vaginal fluid (Cu-Uvin *et al.*, 2000). Indeed, initiation of ART early in infection is associated with a viral load reduction in the infected person and can reduce the rate of transmission to the HIV negative partner. TasP can reduce risk of HIV transmission by up to 96% (Cohen *et al.*, 2011). Furthermore, Rodger *et al.* (2016) reported a zero rate of within-couple transmission from the PARTNER study conducted between 2010 and 2014 in which the HIV-positive partners from 1 166 sero-discordant couples enrolled were put on suppressive ART. Prevention of mother to child transmission programs also emphasise the use of ART for HIV prevention (Connor *et al.*, 1994; Siegfried *et al.*, 2011). Indeed, Townsend and colleagues (2008) showed that ART administration to pregnant HIV-positive women for only two weeks reduced risk of vertical transmission to less than 1%.

Although the working definition of TasP does not include use of anti-retroviral drugs (ARVs) for post-exposure prophylaxis (PEP), pre-exposure prophylaxis (PrEP) and ARV-based microbicides, these strategies have shown promise for biomedical prevention strategies. With PEP, ARVs are taken for a short duration during the initial hours following possible exposure to HIV-1 (Cardo *et al.*, 1997; Henderson and Gerberding, 1989). PrEP in contrast uses ARVs to protect uninfected individuals before exposure, the idea being to interfere with the pathways used by HIV to establish an infection.

Tenofovir disoproxil fumerate (TDF) and TDF in combination with emtricitabine (FTC) (called Truvada®) can prevent HIV replication and the establishment of a funder population. TDF alone showed a 67% (Baeten *et al.*, 2012) and 48.9% (Choopanya *et al.*, 2013) reduction of HIV incidence among heterosexual couples and IDUs respectively while Truvada® demonstrated a 75% HIV incidence reduction among heterosexual sero-discordant couples (Baeten *et al.*, 2012). Others, the iPrEx study for instance showed that Truvada® reduced by 44% the HIV incidence (Grant *et al.*, 2010) while the PROUD study (McCormack *et al.*, 2017) emphasised that the immediate and daily uptake of Truvada® is feasible among a high risk HIV population. Both trials were conducted among MSM.

In contrast, the FEM-PrEP (Van Damme *et al.*, 2012) and VOICE study (Marrazzo *et al.*, 2015), both conducted among women, did not show efficacy of PrEP and were prematurely terminated. Poor adherence to the intervention protocol and the stigma associated with the uptake of ARVs are among reasons hypothesised to explain the failure in these specific trials (Haire, 2015 ; Mack *et al.*, 2014; Van Der Straten *et al.*, 2014). Nonetheless, a trial among MSM and female sex

workers (FSWs) done in Kenya suggested that an intermittent PrEP dosing regimen would be more feasible among higher-risk groups despite low adherence (Mutua *et al.*, 2012). Overall, PrEP using Truvada® is beneficial for HIV prevention efforts. Its use has only been approved in 6 countries - Botwana, Canada, France, Kenya, Peru, South Africa and USA, but many other countries are conducting clinical trials to assess feasibility of PrEP for their public health policies per local contexts. Unfortunately, high cost, low availability and low uptake of Truvada® has been observed as major hindrances for worldwide roll-out (WHO, 2015; Williams and Gouws, 2012).

Maraviroc, another drug tested for use in PrEP, is a HIV entry inhibitor via blockage of CCR5 receptors (Coll *et al.*, 2015). Though some efficacy has been seen in rhesus macaques using a maraviroc based microbicide (discussed later in this review), oral maraviroc did not prevent simian-HIV (SHIV) transmission (Massud *et al.*, 2013). Additionally, Coll *et al.* (2015) recently showed that a single oral dose of maraviroc does not prevent rectal HIV transmission.

MICROBICIDES FOR HIV PREVENTION

The WHO describes microbicides as "compounds applied on the vagina or rectum to prevent STIs, including HIV". They are available in different formulations including gels, suppositories, dissolving films, creams or sponges. Micobicides offer protection by providing a physical barrier between the pathogen and its target cells; by maintaining the natural level of vaginal pH thus enhance the natural vaginal defence mechanism; or by preventing pathogen replication. In this review, we classify microbicides according to whether or not they are ARV based.

First Generation: Non-ARV Based Microbicides

Surfactant Microbicides:

Nonoxynol-9: Nonoxynol-9 (N-9) is a non-ionic detergent and the principal active ingredient in most over-the-counter spermicides. It had been used for contraception since 1950s but the need for a female controlled method to prevent HIV led to clinical trials looking into its effectiveness in a vaginal microbicide. Studies demonstrated that microbicides containing N-9 do not reduce the rate of STIs nor HIV infection (Richardson *et al.*, 2001; Roddy *et al.*, 1998; Kreiss *et al.*, 1992). More dramatically, when used frequently by women at high-risk of infection, N-9 actually increased the rate of genital lesions and risk of gonorrhoeal infection (Richardson *et al.*, 2001). Similarly, a randomised placebo-controlled clinical trial conducted among FSWs from Benin, Côte d'Ivoire, South Africa and Thailand, found that multiple use of N-9 increased lesions and epithelial barrier disruption therefore enhancing HIV-1 infection (Van Damme *et al.*, 2017). In light of these findings, studies on N-9 to prevent HIV-1infection were stopped.

C31G/Savvy: Savvy vaginal gel (C31G) had been shown, *in vitro*, to inhibit *Chlamydia trachomatis* infectivity (Wyrick *et al.*, 1997). Two clinical trials conducted in Ghana and Nigeria to test the effectiveness of a 1% C31G gel to prevent HIV-1 were both prematurely stopped due to futility. The studies cited that use of Savvy caused vaginal irritations which may have led to inflammation of the genital tract and pre-dispose the user to HIV-1 infection (Feldblum *et al.*, 2008; Peterson *et al.*, 2007).

Though surfactants have the advantage of contraception and disruption of virus membrane, failure of N-9 and C31G highlighted that such compounds deleteriously impact healthy cells when used in microbicides.

Blocking and Buffer Microbicides:

Pro2000 and BufferGel: Pro2000 gel is a synthetic naphthalene sulphonate polymer with ability to bind CD4 and block binding of gp-120 (Rusconi *et al.*, 1996) thus prevent attachment and entry of HIV into the cell. Although the gel has been shown to be safe and well tolerated among women (Guffey *et al.*, 2014; Karim *et al.*, 2011; McCormack *et al.*, 2010) and having anti-viral action in laboratory and non-human primate experiments (Bourne *et al.*, 1999); a 0.5% formulation indicated little (Karim *et al.*, 2011) or no (McCormack *et al.*, 2010) protective effect against HIV-1 acquisition in humans. BufferGel, a vaginal gel that maintains an acidic vaginal pH has been shown protective against *Neiserria gonnorhoeae* and *Chlamydia trachomatis* infection *in vitro* and in some animal models (Spencer *et al.*, 2004; Achilles *et al.*, 2002) but not protective against HIV-1 infection in women (Karim *et al.*, 2011) .

Cellulose Sulphate: Cellulose sulphate (CS), an antimicrobial agent also proved disappointing in search for an effective microbicide. Although safe and well tolerated (El-Sadr *et al.*, 2006), it showed no effect against STIs or HIV (Halpern *et al.*, 2008). Indeed, interim analysis of a multi-country trial showed that 13 more participants in a 6% CS treatment arm sero-converted compared to the placebo arm (Van Damme *et al.*, 2008). Later Mesquita and colleagues showed that although CS was not cytotoxic, its use led to rapid and sustained disruption of tight mucosal junctions (Mesquita *et al.*, 2009) and overall actually increasing the risk of HIV-1 infection.

Carraguard: *Carraguard* is a sulphated polysaccharide used as a commercial additive. *In vitro* studies indicated that it could block cell line adhesion suggesting it could prevent mucosal transmission of HIV-1 (Pearce-Pratt and Phillips, 1996). Mice and rabbit models also showed that *Carragaurd* prevented herpes simplex virus-2 (Zacharopoulos and Phillips, 1997) and human papilloma virus (Marais *et al.*, 2011) infection and did not have toxic effects nor cause mucosal irritation (Sudol and Phillips, 2004), but failed to show any efficacy for HIV-1protection in humans (Skoler-Karpoff *et al.*, 2008).

These first generation microbicides did not confer protection against HIV infection and some, in fact, enhanced acquisition by causing epithelial barrier disruption.

Second Generation: ARV Based Microbicides

This new generation of microbicides, also termed 'topical PrEP' are specific to prevent HIV but do not offer protection against other STIs.

Tenofovir-based Microbicides: Overall, from the CAPRISA 004 Microbicide clinical trial to analyse the efficacy of a 1% tenofovir gel formulation, HIV-1 infection reduced by 39% and by 54% among the women who adhered to the study protocol (Abdool Karim *et al.*, 2010). 889 HIV-negative women from South Africa had been enrolled in this double-blind randomised placebo controlled trial and randomly assigned to either 1% tenofovir gel or placebo gel arm. This was the first clinical trial to show that a microbicide could prevent HIV infection bringing hope for biomedical prevention. Recently, it was shown that the composition of the vaginal microbiome of the women enrolled in CAPRISA 004 affected the efficacy of the tenofovir gel (Klatt *et al.*, 2017).
Nonetheless, the FACTS 001 clinical trial also among HIV-negative sexually active women in South Africa, contradicted these findings, with 123 infections occurring during the trial (61 and 62 in the treatment and placebo arm respectively). Tenofovir effectiveness was however higher in about 20% of the women who used the product in more than 72% of their sex encounters (Rees *et al*., 2015). Similarly, both the oral and 1% vaginal gel arms of tenofovir in the VOICE study were discontinued when interim analysis showed that neither formulation provided HIV-1 protection. Poor adherence to the intervention appeared to be the main reason for no effect (Mascolini, 2013). In light of VOICE and FACTS 001 results, it is unlikely that a 1% tenofovir gel will move forward as a microbicide. Adherence is brought out as an issue and the need to design microbicides that are long lasting and/or easier to integrate into the daily lives of women is emphasised.

Dapivirine-based Microbicides: The idea to develop a longer lasting microbicide was pushed forward in two phase III sister clinical trials, the ASPIRE and The Ring Study, conducted in Zimbabwe, Uganda, South Africa and Malawi. Both enrolled, in total, of 4 500 women to study the safety and efficacy of a vaginal ring containing 25mg of dapivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI) (Baeten *et al.*, 2016). The ASPIRE study showed a 27% reduction in HIV-1 incidence among the dapivirine treated group compared to the placebo; while 31% efficacy was observed in The Ring Study. Conversely, post-hoc analysis demonstrated up to 56% protection in women older than 21 years but no protection in younger women in ASPIRE and only 15% protection was observed in younger women in The Ring Study (International Partnership for Microbicides, 2016). Adherence to the intervention, biological differences between young and older women and/or number of sex acts with HIV-1 infected partners possibly explain this difference.
ARV-based microbicides are better at HIV prevention, but adherence is still a major concern. Combining a microbicide with a contraceptive method may provide double-pronged benefit and increase adherence ('After The Ring Study : DREAM', 2017).

Potential Microbicide Bases

Some other products have been tested for use as microbicide bases, some, like maraviroc and glycerol monolaurate, seem promising though more research is required.

Maraviroc: Rhesus macaques exposed to maraviroc vaginally were protected against a high-dose SHIV challenge in a dose dependant manner (Veazey *et al.*, 2010). A phase I trial, conducted to determine the safety and pharmacokinetics of a ring containing maraviroc alone, dapivirine alone, dapivirine-maraviroc combination or placebo, enrolled 48 women from USA and found that the combination ring was safe and well tolerated. However, while maraviroc was detected only in the vaginal fluid and at very low levels in cervical tissue, dapivirine was detected in plasma, vaginal secretions and cervical tissue. The combination ring is being reformulated to increase release of maraviroc (Chen *et al.*, 2015).

Glycerol monolaurate: Glycerol monolaurate (GML), also called monolaurin, is a fatty acid monoester commonly used as a food preservative and emulsifier in cosmetics (Bevilacqua, Sinigaglia and Corbo, 2008; Ruzin and Novick, 2000). It is found naturally in coconut oil (Lieberman, Enig and Preuss, 2006) and human breast milk (Hegde, 2006; Peterson and Schlievert, 2006), thus is considered safe. *In vitro*, GML can inhibit bacterial growth (Peterson and Schlievert, 2006) at low concentrations and block bacterial exotoxin production (Schlievert *et al.*, 2008). GML in a microbicide was first tested in rhesus macaque models and demonstrated neither modification of normal mucosal integrity nor inflammation (Schlievert *et al.*, 2008). Further, Ashley Haase's group showed that GML confers protection against high-doses of vaginally introduced SIV (Haase *et al.*, 2015; Li *et al.*, 2009). This protective ability was associated with GML's capacity to inhibit production of macrophage inhibitory protein (MIP)-3α and the pro-inflammatory cytokine interleukin (IL)-8, thus curtailing cell signalling pathways that recruit CD4 T-cells to the mucosal surface. The efficacy of GML in prevention of HIV infection in humans remains to be demonstrated.

Generally, although microbicides show protection potential, the need to develop a long-term HIV protective biomedical method such as a vaccine remains a public health priority.

VACCINES FOR HIV PREVENTION

Development of a vaccine could be the "final bullet" against HIV infection. Several candidate vaccines have been developed and tested.

AIDSVAX: The VAX004, a phase III double-blinded vaccine trial, randomised 5 095 HIV-negative men and 308 women at high risk of infection to receive intramuscular injections of the recombinant gp-120 vaccine (AIDSVAX B/B; VaxGen) derived from 2 sub-type B HIV strains, or the placebo consisting of alum only (Group, 2005). There was no protective effect, with a 6.7% and 7.0% infection rate seen in the treatment and placebo group respectively. Similarly, another phase III trial by Pitisuttithum *et al.* (2006) conducted in Thailand tested the efficacy of a bivalent subtype B/E recombinant gp-120 HIV-1 vaccine (AIDSVAX B/E; VaxGen) among IDUs. This showed neither efficacy in preventing HIV-1 infection nor ability to impede disease progression.

STEP and Phambili Trials: The Merck Adenovirus Serotype 5 HIV-1 *Gag/Pol/Nef* Vaccine (MRK AD5® HIV-1 *Gag/Pol/Nef*), a DNA-based vaccine, was tested in the double blind STEP (HVTN 502/Merk V520-023) phase IIb trial initiated in 34 sites in the Americas, Australia and the Caribbean. 3 000 HIV-negative individuals at high risk of infection were randomised to receive 3 doses of either the vaccine or placebo at week 0, 4 and 26. Interim analysis indicated that 24 out of 741 infections occurred in the treatment arm and 21 out of 762 in placebo arm, each participant having received only one dose of either, and STEP was stopped. Although this vaccine was shown to elicit an interferon-gamma immune response in 75% of randomly selected samples, those who sero-converted during the study revealed no decrease in viral concentration, contradicting the expectation of a cell-mediated response to kill infected cells and reduce viral load (Buchbinder *et al.*, 2008). The HVTN 503/Phambili Study planned parallel to STEP in South Africa was also halted following results from interim results of STEP (Gray *et al.*, 2011).

Interestingly, analyses from both trials indicated that HIV risk actually increased in the vaccine arms. Being uncircumcised and/or being adenovirus-5 (Ad5) sero-positive prior to vaccination was associated with this increased risk (Duerr, *et al.*, 2012; Gray *et al.*, 2011) and, enhanced activation of the immune system induced by the Ad5 vector shortly after vaccination may have caused increased number of HIV-1 target cells at the mucosal sites. In Phambili, vaccinated women who sero-converted had lower viral load and a slower CD4 T-cell decline compared to those in the placebo arm, suggesting that sex may play a role in HIV-1 vaccine responses.

HVTN 505

This phase IIb, randomised, double-blind, placebo-controlled trial evaluated vaccine candidate in a prime-boost strategy among 2 504 HIV-negative circumcised MSM in USA (Hammer *et al.*, 2013). The regimen was initiated with 3 intramuscular injections of either the vaccine, the VRC-HIVDNA016-00-VP containing 6 separate DNA plasmids including *Gag, Pol, Nef* genes from HIV-1 clade B and *Env* genes from HIV-1 clade A, B and C or placebo over an 8 week period. Twenty four weeks later, participants received a single injection of the boost vaccine consisting of *Gag/Pol* genes from HIV-1 clade B and *Env* genes from clade A, B and C delivered in an Ad5 vector or vector free placebo. The vaccine showed no protection against HIV with 41 new infections (27 in vaccine group and 21 in placebo group) occurring; neither did it reduce viral load in those who were infected.

RV-144

To date, the only promising outcome of a HIV vaccine trial is from the RV-144 phase III clinical trial conducted in Thailand. This canarypox vector vaccine (ALVAC-HIV [vcp1521]) prime, plus the recombinant gp-120 sub-unit AIDSVAX® B/E boost vaccine indicated a 31.2% reduction in rate of HIV-1 infection (Rerks-Ngarm *et al.*, 2009). 16 402 healthy adults, enrolled and randomised, received four injections of either, the prime vaccine at weeks 0, 4, 12 and 24 plus boost immunizations at weeks 12 and 24; or placebo injections at same time points. Although the results were promising, RV-144 did not show an effect on viral load among the individuals who sero-converted. Follow up studies indicated that protection was associated with the production of V2-specific antibodies against V1/V2 area of the viral envelope protein as well as some efficacy mediated by neutralising antibodies (Zolla-Pazner *et al.*, 2013; de Souza *et al.*, 2012; Karasavvas *et al.*, 2012; Montefiori *et al.*, 2012).

HVTN 702

Ongoing in South Africa, is a phase IIb/III clinical trial which aims to test the tolerability, safety and efficacy of ALVAC-HIV [vcp2438] plus a bivalent Subtype C gp-120/MF59 candidate vaccine in HIV-negative adults (Global Advocacy for HIV Prevention, 2017). Findings will provide more information to help perfect a much needed HIV-1 vaccine.

Despite the number of candidate vaccines tested, some showing efficacy, none is ready for licensure as none offers a threshold of protection high enough to recommend for a large scale roll-out. CAPRISA 004 and RV-144 proved that a microbicide or vaccine against HIV is feasible, however further research is required to augment their efficacy.

NEW FRONTIERS FOR BIOMEDICAL APPROACHES TO HIV PREVENTION

Overwhelming evidence that increased immune activation and inflammation are risk factors for HIV infection is documented (Masson *et al.*, 2014; Card, Ball and Fowke, 2013; Mitchell *et al.*, 2008; Johnson and Lewis, 2008; Rebbapragada *et al.*, 2007; Corey *et al.*, 2004; Corbett *et al.*, 2002; Sturm-Ramirez *et al.*, 2000; Giorgi *et al.*, 1999, 1993; Liu *et al.*, 1998). This aspect is also demonstrated through microbicide (Haase *et al.*, 2015; Masson *et al.*, 2015; Naranbhai *et al.*, 2012; Lozenski *et al.*, 2012; Li *et al.*, 2009; Fichorova, 2004; Fichorova, Tucker and Anderson, 2001) and vaccine studies (Duerr, *et al.*, 2012). The link between HIV infection and immune activation is also emphasised among HIV-exposed seronegative (HESN) individuals (McKinnon *et al.*, 2015; Card, Ball and Fowke, 2013; MacKelprang *et al.*, 2012; Lajoie *et al.*, 2012; Songok *et al.*, 2012; McLaren *et al.*, 2010; Card *et al.*, 2009; Jennes *et al.*, 2006; Koning *et al.*, 2005; Kaul *et al.*, 1999; Fowke *et al.*, 1996). HESN demonstrate a lower baseline of immune activation than would be considered normal, a state called immune quiescence (Card, Ball and Fowke, 2013). With this in mind, could decreasing baseline immune activation be a useful element for HIV prevention?

Certain compounds known to alter the body's immune system have been tested for their effects on HIV, for instance, type 1 interferon (IFN) blockers such as chloropromazine, bafilomycin and chloroquine which lower the production of IFNs and pro-inflammatory cytokines. Also, chloroquine (CQ) and its analogue hydroxychloroquine (HCQ) been shown to act as anti-HIV agents (Martinson *et al.*, 2010; Beignon *et al.*, 2005; Karres *et al.*, 1998). *In vitro* studies indicated that CQ decreases formation of pro-viral DNA (Fesen *et al.*, 1993) as well as inhibits HIV-1 integrase and Tat-mediated trans-activation of HIV-1 long term repeats (LTRs) (Savarino *et al.*, 2001); thereby altering the immunogenic properties of gp-120 and decreasing HIV-1 production. Additionally, CQ can inhibit metabolism of

arachidonic acid thereby inhibit Tat-mediated LTR driven gene expression of HIV-1 (Jiang, Lin and Chen, 1996). Piconi and colleagues (2011) showed that 6 month treatment with HCQ led to a significant decrease in proportion of proliferating lymphocytes (CD4+Ki67+) and activated monocyte (CD14+CD69+ cells); as well as increases of naive and activated T-regulatory levels in HIV-infected immunologic non-responders. This study also demonstrated reduction of IFN-α secreting pDCs plus interleukin (IL)-6 and TNF-α producing CD4+ and CD14+ cells.

Another group of compounds shown to reduce chronic immune activation are Cyclooxygenase type 2 (COX-2) inhibitors (Pettersen *et al.*, 2011). Inhibition of COX-2 leads to decreased production of pro-inflammatory cytokines. An example is acetylsalicylic acid (aspirin) which decreases of pro-inflammatory prostaglandin E2, thromboxane B2 and IL-2 production (Coe, Denison and McCabe, 2011) and increases production of lipoxin A4 (LXA4) and 15-epi-LXA A4 which are anti-inflammatory (Ariel *et al.*, 2003; Planagumà *et al.*, 2002). The effect of these on HIV is however yet to be investigated.

Yet another group studied for suitability to reduce immune activation are statins (otherwise called 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors) for example rosuvastatin and atorvastatin, drugs which are used in cardiovascular disease management. Administered as a short term regimen, a high dose of atorvastatin was seen to reduce systemic activated CD4+ and CD8+ lymphocytes expressing cell activation marker HLA-DR (Ganesan *et al.*, 2011). Low dose rosuvastatin on the other hand showed no effect on T cell activation markers, suggesting that reduction of immune activation by statins is dose dependent (Weijma *et al.*, 2016).

This concept of modulation of the body's immune system to induce quiescence is not far-fetched and may be a possible novel facet to augment biomedical strategies for HIV prevention particularly among HIV-high-risk groups such as FSW and MSM.

Conclusion

Preventing HIV infection remains the foremost option to curb the HIV/AIDS epidemic. Although behaviour change strategies remain at the core, it is important to research into improving the efficacy of biomedical methods available and to develop novel modes of prevention. Strategies such as induction of Immune quiescence could add to the biomedical arsenal in the fight against HIV, particularly for key populations

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