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Inducing Immune Protection Against *Trichomonas vaginalis*: A Novel Vaccine Approach to Prevent HIV Transmission

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1. Introduction

Human immunodeficiency virus (HIV) infection is a pandemic that affects all parts of the globe. Current treatments fail to cure disease and for this reason there is significant interest in producing a vaccine to prevent HIV transmission, but clinical trials have proved disappointing. For this reason it is important to consider alternative measures to control incidence and prevalence of the disease.

Trichomonas vaginalis is a highly prevalent and under-diagnosed sexually transmitted infection that facilitates transmission of and susceptibility to HIV infection (McClelland et al., 2007; Mavedzenge et al., 2010). Although current treatment is effective the disease is still poorly controlled and there are concerns about increasing levels of drug resistance (Upcroft & Upcroft, 2001). Efforts to research disease mechanisms and immune response with consideration to a rational vaccine design approach should be investigated as a potential method to reduce global incidence of *T. vaginalis* infection.

A reliable murine model of *T. vaginalis* infection has been established with symptoms in female mice mimicking those seen in women (from vaginitis/vulvitis and discharge to asymptomatic but culture-positive for infection). Using this model it has been shown that vaccinating mice (by injection of trichomonad cells with adjuvant) protects the animals from subsequent vaginal infection (Abraham et al., 1996). By studying immune responses in mice, factors that are critical for immunological protection can be elucidated to create a "blueprint" for an effective human vaccine.

Herein we provide an overview of the current understanding of *T. vaginalis* infection and epidemiology, methods of diagnosis and treatment, and implications of animal models for understanding disease mechanisms . We discuss how and why current *T. vaginalis* treatment protocols fail to control infection incidence with consideration as to how a *T. vaginalis* vaccine could overcome these obstacles and reduce disease burden. The association between *T. vaginalis* and HIV is examined and the potential for reducing HIV infection rates by lowering *T. vaginalis* incidence is elucidated.

A vaccine against *T. vaginalis* would provide long term protection that could be more successful than treatment in controlling the spread of this very common disease. As *T. vaginalis* infection is a clear risk factor for HIV acquisition, it is our belief that this approach would also be effective in ameliorating HIV incidence and prevalence, especially in areas such as South and Southeast Asia and sub-Saharan Africa where HIV and *T. vaginalis* are endemic (United Nations, 2009; World Health Organization, 2001).

2. *Trichomonas vaginalis*

2.1 Morphology

The basic structure of *T. vaginalis* as reviewed in Petrin et al. (1998) and Heine & McGregor (1993) is best described as a 10-20 µm ovoid organism with four free-moving flagella located at the anterior portion, and one recumbent flagellum attached to the body of the cell by a membrane that forms an axostyle running longitudinally from the anterior portion to the posterior forming a pointed tip. The flagella and undulating membrane contribute to the organism's characteristic jerky movements visualized under a common laboratory light microscope. Within the protozoan resides a nucleus with six chromosomes, a developed Golgi complex, but is devoid of mitochondria, peroxisomes or glycosomes, so instead contains hydrogenosomes typical of anaerobic protozoa and fungi. With respect to metabolic processes the parasitic nature of *T. vaginalis* owes to its inability to synthesize many nutrients and thus implicates a significant contribution of scavenged nutrients from hosts to survive (Heine & McGregor, 1993).

2.2 Genetics

Recently a draft genome sequence has been completed (Carlton et al., 2007) revealing a genome of approximately 160 Mb containing a core set of roughly 60,000 genes although it is suggested 39 Mb is repetitive genomic information as a result of enormous gene expansions. Important information will be derived from this data especially since gene regulation is not well understood and even now novel core promoter elements are being identified (Gomez et al., 2010; Smith et al., 2011) as well as hypothetical surface proteins from proteome analysis (de Miguel et al., 2010). Hypothetical surface proteins are of particular interest for extracellular parasites functioning to establish and maintain infection, and may shed light on current issues of classifying phenotypic differences for variable clinical presentation between hosts (Smith et al., 2011).

2.3 Epidemiology

T. vaginalis is an extracellular, anaerobic, parasitic protozoan that is the cause of trichomoniasis, the most common non-viral, curable STI with global incidence of at least 174 million cases per year (WHO, 2001), likely an immense underestimation of actual incidence. Nevertheless, to put this number into relative terms of other curable STI the global incidence of syphilis, chlamydia and gonorrhoea as reported by WHO (2001) were 12 million, 92 million and 62 million, respectively. The majority of cases are localized in regions of low income or lack of resources, especially health care. Other risk factors include *Neisseria gonorrhoeae* infection, *Chlamydia trachomatis* infection, risky sexual behaviours, older male partners (in terms of heterosexual couples), potential for non-sexual transmission by cultural habits such as shared bathing water, new or multiple sex partners, a history of STI, exchange of sex for payment, and drug use (Crucitti et al., 2011; Krashin et al., 2010; Sutton et al., 2007; Workowski & Berman, 2010).

2.4 Trichomoniasis

T. vaginalis resides in the squamous epithelium of the genital tract of both females and males with prevalence primarily within the reproductive years. General areas of infection in males include the urethra, external genitalia, prostate and epididymis. The vagina is the area most

commonly infected for females though it should be noted that other areas of infection include the Bartholin's, Skene's and periurethral glands, bladder and cervix (Heine & McGregor, 1993; Petrin et al., 1998). The infection is followed by an incubation period prior to onset of symptoms, if any at all, with persistent infection commonly occurring in females whereas eventual resolution occurs in males whom mostly serve as carriers and spread the infection to other partners (Petrin et al., 1998; Van Der Pol et al, 2005).

A plethora of possible symptoms surrounds *T. vaginalis* infection. Rarely are all symptoms present nor are typical symptoms easily distinguishable from other urogenital infections. Additionally up to 50% of infected females and greater numbers in males are asymptomatic (Fouts & Kraus, 1980, as cited in Cudmore et al., 2004; Pastorek et al., 1996). While men and women usually present with malodorous discharge from the infected areas the most significant burden is found in women who may present with any of the following; high vaginal pH, bloody mucus, colpitis macularis, and vulvitis. Infection is associated with pelvic inflammatory disease, birth complications including premature rupture of the placental membrane, premature labour, low average birth-weight, and infertility, and increased transmission and contraction of HIV (Cotch et al, 1997; Mavedzenge et al., 2010; McClelland et al., 2008; Moodley et al., 2002; Pastorek et al., 1996; Wølner-Hanssen et al., 1989).

2.4.1 Treatment of trichmoniasis

Lossik (1990) describes the basics of metronidazole, a chemically modified form of the natural *Streptomyces* product azomycin from the family of nitroimidazoles, first synthesized in 1957 and finally marketed in 1960. Metronidazole is effectively administered as a single 2 g dose or 500 mg twice daily for seven days with average cure rates of 96% and 92%, respectively. Side effects are minimal and more adverse effects are the result of very high dosage and longer duration (Lossik, 1990). Upon diagnosis and treatment – typically females are diagnosed as male partners are less likely to observe or report symptoms – it is encouraged that sexual partners be tested and treated in concert as often these individuals are infected as well (up to 70% of male partners are also infected as reported by PCR testing in Seña et al., 2007). The treatment of trichomoniasis with this drug is highly effective although 5-10% of *T. vaginalis* isolates exhibit some degree of resistance as assayed in vitro (Upcroft & Upcroft, 2001).

Five years after the discovery of metronidazole the first metronidazole-refractory case of *T. vaginalis* isolated from a female patient was reported by Robinson (1962, as cited in Lossick, 1990). To avoid future difficulties with metronidazole resistance clinical and laboratory generated drug resistant isolates are under study to determine the mechanisms of resistance that can arise or have arisen (Upcroft & Upcroft, 2001). Alternatively, a *T. vaginalis* vaccine would sidestep the necessity to discover potential drug replacements in the event of epidemic resistance.

2.5 Phenotypic variance of clinical disease

In an attempt to define the phenotypic differences between clinical isolates causing symptomatic disease versus asymptomatic disease a number of areas are under investigation regarding host immune response and parasite-host interactions.

2.5.1 Host immune response

Scott et al. (2005) demonstrated that a symptomatic isolate of *T. vaginalis* induced only an IL-10 response in dendritic cells while a more diverse IL-12, IL-10 and IFN-α repertoire was

produced in response to selected infectious mucosal bacteria. Within the findings a potential relationship is noted between an IL-10 only response and chronicity of infection. IL-10 alone contributes to inhibition of T helper type 1 (Th1) immunity and favours a Th2 response (Banchereau et al., 2000, as cited in Scott et al., 2005). Similar results of a lack of IL-12 induction in macrophages were previously reported by Chang et al. (2004). On the other hand, cytokines related to Th1 type response (IL-2 and IFN-gamma) have been noted to be more prevalent in the sera of mice infected with asymptomatic isolates than symptomatic isolates (Malla et al., 2007; Paintlia et al., 2002). Similar results have been found in other protozoal disease cytokine studies suggesting that in these cases Th1 mediated response may regulate disease and prevent overt clinical symptoms but not abolish infection (Agarwal et al., 1999, Bayraktar et al., 2005 and Campbell & Chadee, 1997, all as cited in Malla et al., 2007).

Yadav et al. (2005) investigated immunoglobulin kinetics of intravaginal trichomoniasis in a mouse model with asymptomatic and symptomatic clinical isolates. IgM, IgG (subclasses 1, 2a, 2b and 3) and IgA were measured in serum and from vaginal washes from mice infected with asymptomatic and symptomatic isolates. Titers of IgG, IgG1 and IgM of vaginal wash and serum samples were significantly greater in symptomatic infected mice than asymptomatic mice, while IgA responses were not statistically different for serum or vaginal washes of either asymptomatic or symptomatic isolates. These results are mostly in line with vaginal wash data from symptomatic infections in women showing IgG and IgA at detectable levels versus undetectable levels in asymptomatic women (Alderete, 1984, as cited in Yadav et al., 2005). Data from Paintlia et al. (2002) found greater IgA levels in both vaginal wash and serum samples of asymptomatic isolates infected in mice contradicting the aforementioned findings. These results may indicate complications with the model of study or are simply the intricacies of trichomonal infection. Thus, some antibodies may provide a method of predicting the severity of infection. Whether these findings are host dependent or mediated by phenotypic variance of *T. vaginalis* is yet to be elucidated.

2.5.2 Parasite-host interactions

Contact-independent mechanisms of damage correlated to symptomatic states of infection involve soluble factors shed from *T. vaginalis* including cell detaching factor (CDF), cysteine proteases and a haemolytic factor that is reliant on specific elevated vaginal pH in the range typically observed in clinical disease (Alderete & Garza, 1984; Fiori et al., 1996; Garber & Lemchuk-Favel, 1990).

Gene regulation is influenced by contact with epithelial cells (Kucknoor et al., 2005) and cytoadherence has been noted as a better predictor of in vivo pathogenicity than cytotoxicity by soluble factors (Escario et al., 1995). Unfortunately the pathogenic role of adhesion proteins such as AP65, AP51, AP33 and AP23 that have been associated with epithelial cell binding of *T. vaginalis* (Alderete & Garza, 1984; Arroyo et al., 1992) have not conclusively been elucidated. Midlej & Benchimol (2010) suggests that adherence may aid phagocytic capability and disruption of monolayers in which *T. vaginalis* literally mechanically disassembles and phagocytoses membranes of epithelial monolayers in vitro similar to previous findings in amoebae and macrophages during ingestion of tumour cells (Chambers & Weiser, 1969, as cited in Midlej & Benchimol, 2010; Martinez-Paolmo et al., 1985, as cited in Midlej & Benchimol, 2010). Particularly, whole, viable cells are not phagocytosed yet destruction of epithelial cell layers is observed suggesting necrotizing ability of *T. vaginalis*. Interestingly within Midlej & Benchimol's study (2010) an actin polymerization inhibitor significantly abrogated adherence while cytotoxicity remained relatively unaffected.

Another mechanism of interest is the availability of iron and its role in regulating immune evasion, and expression of adhesins and cysteine proteases (Lehker et al., 1991; Lehker & Alderete, 1992). Alternative pathway complement lysis allows destruction of trichomonads under low iron conditions assessed by Alderete et al. (1995). Upon supplementation of media with high levels of iron a cysteine proteinase capable of removing surface bound C3 is upregulated. Still not all cysteine proteases are upregulated as found in Kummer et al. (2008). Herein, the data provides an inverse correlation of iron abundance and presence of CP2, CP3, CP4 and CPT (collectively referred to as CP30) which are involved in apoptosis of human vaginal epithelial cells. Kummer et al. (2008) suggests this particular apoptotic mechanism may play a role in iron acquisition and is self-regulating upon iron uptake. Alvarez-Sánchez et al. (2007) also provide a negatively regulated soluble factor, CP65, under high iron conditions.

Understanding phenotypic variance will aid in understanding of the disease and elucidation of possibly novel mechanisms of regulation, as well as contribute to the strategies employed for development of a vaccine, a goal of ongoing research that will be discussed later.

2.6 Diagnosis

Before assessing the current diagnostic techniques available it is imperative to emphasize the difficulties of arriving at the diagnostic stage. Using a clinical syndromic approach a significant number of asymptomatic cases are missed. By not testing for nor treating asymptomatic infected individuals this enables the spread of disease and the lack of diagnosis results in underreported statistics of infection worldwide (Yin et al., 2008). Furthermore, in a prospective study Wiesenfeld & Macio (1999) found the available diagnostic tools such as simple wet mount microscopy, pH test or whiff test were often not used even under clinical suspicion of trichomoniasis. Ignoring the latter issue yet another problem arises. Diagnosis of cases investigated from clinical suspicion of trichomoniasis are at mercy of low sensitivity of current diagnostic standards as recent evaluations over the past decade have come to find (Lusk et al., 2010; Roth et al., 2011; Seña et al., 2007; Van Der Pol, 2007; Wendel et al., 2002). The most prevalent and most promising techniques will be reviewed below while a more detailed overview of guidelines for laboratory diagnosis and the methodology can be found in Domeika et al. (2010).

2.6.1 Culture and wet mount microscopy

Culture is considered the gold standard for diagnosis of *T. vaginalis*. Culture liquid is supplemented with antibiotics and samples are obtained from various locations such as vaginal/urethral discharge and swabs of known areas of infection. This technique requires as little as 10^2 trichomonads/mL (Garber, 2005). Unfortunately bacterial contamination remains an issue as well as lag growth phases of *T. vaginalis*. Additionally, this method is expensive and time consuming (Domeika et al., 2010) despite the availability of commercial culture systems (InPouch TV system: BioMed Diagnostics). Studies have found sensitivities ranging between 75-83% and specificity near 100% (Huppert et al., 2007; Nye et al., 2009; Wendel et al., 2002).

Wet mount is an attractive diagnostic tool due to its simplicity and cost effectiveness, and is consequently the most widely used (Huppert et al., 2007). This technique requires that samples are placed in physiological sterile saline and kept warm for immediate viewing under a common laboratory microscope. Positive detection is assessed by visualization of

trichomonads exhibiting characteristic jerky movements (Domeika et al., 2010). Due to the requirement of at least 10^4 trichomonads/mL (Garber, 2005) this technique is not viable for urethral swab samples from males who typically yield low organism counts. Moreover, incorrect temperature or too much time elapsing between sampling and assessment results in loss of movement creating difficulty of differentiation from lymphocytes or nuclei of vaginal epithelial cells present in the sample (Garber, 2005). Sensitivities range from 52-61.5% and specificity near 100% (Huppert et al., 2007; Nye et al., 2009; Van Der Pol et al, 2006; Wendel et al., 2002).

2.6.2 Nucleic acid amplification test and transcription mediated amplification

Nucleic acid amplification testing (NAAT) and transcription mediated amplification (TMA) are recent, fairly labour intensive, highly sensitive but non-FDA approved diagnostic tools for detecting *T. vaginalis* which have been based on modifications of previous NAAT and TMA tests for infections such as chlamydia or gonorrhoea (Domeika et al., 2010; Van Der Pol et al, 2006). These tests may be conducted years after sample collection depending on proper storage conditions unlike wet mount which results in much less sensitivity unless maintained under strict time and temperature conditions (Van Der Pol et al, 2006). Despite high sensitivity for both male and female samples (Seña et al., 2007), greater than wet mount and culture (Crucitti et al., 2003; Lusk et al., 2010; Roth et al., 2011), in the range of 70-98% and specificity from 94-100% (Huppert et al., 2007; Nye et al., 2009; Seña et al., 2007; Wendel et al., 2002) this method is problematic as it is not point of care and remains unconfirmed for use in clinical settings.

2.6.3 Rapid antigen testing

Rapid antigen testing presents as probably the most promising technique despite requiring adequate technical skills and slightly less sensitivity than NAAT or TMA since it is inexpensive and can be employed at point of care (Domeika et al., 2010; Huppert et al., 2007). Also, this diagnostic tool is more sensitive than wet mount and culture microscopy. The rapid antigen test employed in Huppert (2007) obtained a sensitivity of 90% and specificity of 100%.

3. Murine model of infection and vaccination

An effective model for the study of *T. vaginalis* is pertinent not only to understand the disease in context of the findings discussed so far, which only skim the surface of the actual breadth of scientific knowledge for each topic, but also to encourage development of vaccine strategies especially given the underestimated prevalence of the disease, the largely asymptomatic population group that remains untreated and the lack of available drug treatment in low resource settings. Within this frame of mind a mouse model modified to its current state by our lab holds important implications for study of *T. vaginalis* pathogenicity and also serves as a vaccination model.

The murine model has been in development for some time coming to fruition as successfully demonstrating inducible protection upon vaccination against intravaginal challenge of *T. vaginalis* in BALB/c mice (Abraham et al., 1996).

First, estrogenization studies in rats appear to affect APC presentation in vaginal cells and uterine stromal cells negatively while increasing antigen presentation in the uterine epithelial cells through mechanisms not thoroughly understood (Wira et al., 2000).

Nevertheless estrogenization is pivotal for increasing experimental infection rates in mice. It is hypothesized estrogenization may induce a state of estrus that is more permissive to infection (Meysick & Garber, 1992). This hypothesis is in line with results also within Meysick & Garber (1992) that infection rates were increased, but duration was unaffected, thus a factor at timepoint zero of infection likely mediates the findings. Additionally, in the same study the vaginal flora of the mouse remained unaffected by treatment, an important factor as we will see in other studies. Interestingly as a side note estrogenization in mice affects CDF, a soluble cytotoxicity element secreted by *T. vaginalis* (Garber et al., 1991). This may complicate findings when used as a disease model.

Next, particular elements of the human vaginal environment have been thought to play a role in infection as noted by a decrease of *Lactobacillus* species levels and an associated increase of pH. Thus, through experimental inoculation of *Lactobacillus acidophilus* the mice would reflect more appropriately the human vaginal environment in terms of presence of lactobacilli and an associated pH decrease produced by products excreted by *L. acidophilus* (McGrory & Garber, 1992). With low percentages of natural incidence of lactobacilli in mice vaginas, an elevated pH and the disruption of these variables observed in human vaginas (Meysick & Garber, 1992) this factor of colonization was investigated. McGrory & Garber (1992) showed a significant increase in duration of trichomonal infection at day 24 post infection – 63-75% infected lactobacillus inoculated versus 0-25% infected controls. This suggests lactobacilli facilitate prolonged *T. vaginalis* infection.

Finally, the vaccination model (see Abraham et al., 1996) utilizes subcutaneous whole cell vaccination emulsified in adjuvant. While unfortunately the current adjuvants used (Freund's complete adjuvant and Freund's incomplete adjuvant) are not safe for human use, current preliminary work with human-safe FDA approved adjuvant aluminum hydroxide (Alhydrogel) has shown induction of serum immunoglobulin responses significantly greater than natural infection (unpublished observations). While this result is not entirely surprising it simply adds to validation for use of the current mouse model as a candidate for experimental vaccine development. Furthermore these mice when infected fall into categories of asymptomatic and symptomatic infection. Of the latter, typical symptoms include vulvitis, vaginitis and vaginal discharge.

Another similarity to human infection within the mouse model is that drug treatment resolution of infection and rechallenge does not confer any level of immune protection in mice as seen in humans (Abraham et al., 1996). On the other hand healthy skepticism is warranted in use of this current mouse model as suggested by Corbeil (1995). The actual pathogenic interactions of the murine vaginal epithelial cells with *T. vaginalis* are not characterized and similar protein binding adhesins mechanisms have not been demonstrated (Corbeil, 1995) which as previously noted was a significant correlate to symptomatic disease. Instead Corbeil suggests the use of a *Tritrichomonas foetus* bovine model.

4. Vaccinating against trichomonads

4.1 Bovine vaccine against *T. foetus*

The *T. foetus* bovine model cattle are a natural host to the parasite and infection occurs through natural means. In addition to its well characterized disease states a commercial vaccine is already available (Fort Dodge Laboratories, Fort Dodge, Iowa) based on previous

work of immunization of bulls with whole cell or membrane fraction in oil adjuvant (Clark et al., 1983, as cited in Corbeil, 1995; Clark et al., 1984, as cited in Corbeil, 1995) and partial immunity in cows (Herr et al., as cited in Corbeil, 1995; Kvasnicka et al., 1989; Kvasnicka et al., 1992, as cited in Corbeil, 1995). The vaccines are not 100% protective, but significantly reduce transmission and infection rates among herds (Corbeil, 1995). Still this model may not be as attractive due to costs associated with purchase and husbandry of these animals whereas large sample numbers are obtainable, handling is easier and costs are within regular laboratory budgets to maintain mice. Also, while the host may be natural differences exist between *T. vaginalis* and *T. foetus* such as their ability to specifically induce lysis of human vascular endothelial cells and bovine vascular endothelial cells, respectively (Singh et al., 2004). As a last ironic note of difference it is the females that generally clear infection and the males that are asymptomatic carriers of *T. foetus* infection (Corbeil, 1995).

4.2 Developing a human vaccine against *T. vaginalis*

T. vaginalis presents an interesting challenge for providing immunity. It requires both mucosal immunity and consideration of mechanisms surrounding chronicity. Notably a vaccine obstacle is the surface heterogeneity of *T. vaginalis* inadvertently downregulating potent immunogenic proteins or glycoproteins (Alderete et al., 1986). Between phenotypic expression differences and strain differences between asymptomatic and symptomatic isolates an immunogen will be required to elicit robust immune response against a variable spectrum of antigens upon infectious challenge. The immunological activation necessarily must be sufficient enough to provide resolution without drug treatment especially in females.

Theoretically speaking the approach may seem easy such as vaccinating against a protein involved in sequestering resources given the parasitic nature of the infection. Even if a recombinant immunogenic protein can be purified and produced consistently the delivery method is problematic as many routes of vaccination exist. While some routes are more desirable than others, depending on the adjuvant of choice the options to produce an appropriate response via a given route become far and few between. While applying our expanding knowledge of adjuvant mechanisms and adjuvant-mediated immune response skew (O'Hagan & De Gregorio, 2009) may seem an obvious path, it neglects to consider the importance of understanding of the infection processes that mediate immune evasion or are the reason natural immunity fails in the first place. This gap emphasizes our need for a consistent laboratory model for study of pathogenesis and the mechanisms of function to facilitate adjuvant selection and even antigen selection as a subunit vaccine alone may not work. Lastly, in design of a vaccine we must consider the target demographic. In this case there is a strong need to service low resource communities especially those sub-Saharan Africa areas with high incidence and prevalence of both *T. vaginalis* and HIV infection (World Health Organization, 2001).

Progress in development of a bovine vaccine rather than a human vaccine has been strongly driven by economical factors of commercial farming involving loss of calves in utero (Kvasnicka et al., 1989). If it is commercial revenue or cost associated with the disease that drives funding for research then one must consider the 1.52-2.05 fold increased risk of HIV-1 acquisition (Mavedzenge et al., 2010; McClelland et al., 2008) and the costs associated with drug therapy of both trichomoniasis and HIV.

5. Rationale for a human *T. vaginalis* vaccine

5.1 Failure to control *T. vaginalis* with current treatment

The current treatment for trichomoniasis is oral metronidazole or tinidazole, either as a single 2g dose, or 500mg twice a day for 5 to 7 days (WHO, 2003). Treatment of a patient's current sexual partners has often been recommended but there is some question as to the efficacy of partner therapy. The Centers for Disease Control and Prevention (CDC) do not recommend patient delivered partner treatment (PDPT) for trichomoniasis as they have not found sufficient evidence that PDPT significantly impacts rates of *T. vaginalis* infection (Centers for Disease Control and Prevention, 2006). Additionally, there are barriers associated with PDPT. Having multiple partners or a new partner are predictors for trichomoniasis (Peterman et al., 2006), so PDPT may be ineffective as it may be difficult or undesirable to provide multiple partners with treatment, and a partner obtained after treatment has been completed obviously could not have been the source of initial infection and therefore will not receive treatment. Additionally, a study of HIV positive women who were provided with PDPT showed that 25% did not deliver treatment to their partners. Reasons for not delivering medication included being unable to contact a partner, not wanting to see a partner again, and being afraid of a partner's reaction. Fear of a partner's reaction was not limited to revealing *T. vaginalis* infection, but was also associated with having a partner who was unaware of the woman's HIV infection status (Gatski et al., 2010). This is particularly disturbing in light of the fact that the presence *of T. vaginalis* can lead to an increased risk of the partner contracting HIV, while at the same time ignorance about HIVpositive status may mean that the partner is more willing to engage in unprotected sex.

Because trichomoniasis is endemic in resource-limited settings, diagnosis is generally made purely on the basis of symptoms without any clinical testing. Syndromic treatment then is prescribed based on the most likely cause of illness. Because the symptoms of *T. vaginalis* infection are similar to other non-ulcerative STIs (urethritis in men, vaginitis and discharge in women) (Petrin et al., 1998) the disease is frequently misdiagnosed and the inappropriate drug is prescribed. Despite of the fact that WHO guidelines indicate metronidazole or tinidazole therapy is recommended in all cases of vaginal discharge (WHO, 2003), trichomoniasis is still under-diagnosed and under-treated.

A study in India showed that using the relatively inexpensive InPouch culture kit to test for *T. vaginalis* at the point of care increased would have increased the correct treatment of trichomoniasis from 51% (syndromic treatment, no testing performed) to 82% (based on InPouch results) (Madhivanan et al., 2009). Unfortunately, culture testing requires 3 to 7 days of incubation to confirm the presence or absence of trichomonads, and this time frame may not be acceptable to patients who need to travel to reach medical facilities.

Another problem with syndromic management of trichomoniasis is that treatment guidelines are clear for women only. In India, a country where metronidazole treatment for vaginal discharge is part of syndromic management, high rates of *T. vaginalis* infection were still found in women, and also in many men. Current guidelines recommend treating for trichomoniasis in men only if symptoms of urethritis persist after treatment for gonorrhoea and chlamydia (WHO, 2003). Introducing metronidazole as a part of syndromic treatment for men presenting with non-ulcerative genital infection has been recommended (Becker et al., 2010), however this will still not address the problem of asymptomatic carriers.

Poor control of trichomoniasis is not solely a problem in developing countries. A study in the United States showed that the prevalence of *T. vaginalis* infection is approximately 3% in

women between the ages of 14 and 49. This infection rate doubles in the poorly educated and economically disadvantaged, and nearly quadruples in black women (Allsworth et al., 2009). Additionally persistent, subclinical *T. vaginalis* infections have been reported even after seemingly successful treatment. A study on HIV positive women diagnosed with trichomoniasis showed that despite reported compliance with metronidazole treatment regimen and putative successful cure (negative InPouch culture), a number of women tested positive for *T. vaginalis* infection 3-6 months later, despite reporting no sexual contact in the intervening time (Gatski & Kissinger, 2010).

Drug resistance to nitroimidazoles such as metronidazole and tinidazole has also been reported in 5-10% of clinical specimens (Upcroft & Upcroft, 2001). As there are currently no effective non-nitroimidazole treatments for trichomoniasis, drug resistant *T. vaginalis* must be treated by increasing medication dosages, which often leads to increased adverse effects. If these adverse reactions become severe enough to force cessation of therapy, trichomoniasis can become a chronic condition (Cudmore et al. 2004).

5.2 Other issues with treatment to control *T. vaginalis*

Sexually transmitted infections such as trichomoniasis are societal as well as medical problems. In order to successfully control the disease the personal, social, and cultural barriers associated with dealing with STI need to be addressed.

5.2.1 The education risk factor

Accurate and useful information on STI can be difficult to obtain. A study done with students (aged 13-16, male and female) in the United Kingdom showed that STI were recognized as a serious health problem. However, many of the teenagers were ill- or misinformed about the names of common STI, how to identify a possible infection, where to seek treatment, etc. (Garside et al., 2001). Lack of education has clearly been shown to be a risk factor for acquiring STI. Unfortunately education programs are not available in many areas where HIV and trichomoniasis are endemic due to reasons such as lack of finance and resources, geography, and cultural or personal discomfort about discussing sexuality and STI. As such, the importance of protecting those with little opportunity to access information about STI cannot be underestimated.

Lack of information and awareness regarding STI has been shown to lead to delays in seeking treatment for medical issues involving the genitals. Participants in a study in rural Zimbabwe had little awareness that having an STI could increase their risk of contracting HIV. Men were more aware of the link between STI and HIV (18% of men vs 5 % of women) and this knowledge was associated with seeking treatment more promptly upon noticing symptoms of genital disease. However many men (36%) and the majority of women (70%) ignored symptoms of urethral/vaginal discharge or discomfort, or lower abdominal pain for a week or more before seeking treatment (Gregson et al., 2001). Given the fact that trichomoniasis and other STI have been linked to sequelae such as infertility and adverse pregnancy outcomes, delays in seeking treatment puts reproductive health at risk.

Education about STI in the general population is not the only issue, part of the problem can stem from the lack of healthcare workers specialized in dealing with sexual issues and diseases. In many parts of the world specialist physicians are rare and general practitioners may not have sufficient background, or simply not be comfortable discussing "intimate" issues, especially with the opposite sex. Women are often more comfortable dealing with

other women when discussing sexual issues, but a study in Bangladesh found that female healthcare workers were often uncomfortable discussing sexuality or performing genital exams (Gibney et al., 1999). Because of the embarrassment, social implications, etc. often attached to the subject of STI, an open discussion between a patient and healthcare provider can be difficult when medical personel are clearly uncomfortable with the subject. Patients may be less forthcoming about their symptoms and less likely to seek treatment if healthcare workers appear to be judgemental or reluctant to provide information and care.

5.2.2 Cultural barriers

There is a nearly universal stigma attached to having an STI. Sex and sexuality are generally considered to be very personal issues and seeking treatment for genital disease involves speaking about private matters. In addition reluctance to seek treatment can stem from fear of being associated with promiscuity and negative social behaviours, which are often linked with STI. A study of pregnant women in India showed that although the majority of women stated they were willing to be tested for HIV, they were also highly concerned about the reactions of their husbands, families, and community should it be found that they were seropositive. Additionally, not breastfeeding (recommended to prevent maternal-child HIV transmission) was widely believed to be a sign that a woman was a bad mother or had been unfaithful to her husband (Rogers et al., 2006).

Women in particular are often reluctant to speak about genital health issues, one study cites "shyness" as the single biggest barrier in seeking STI treatment (Gibney et al., 1999). A study of pregnant women in Nairobi found that over a quarter of women refused to answer portions of a health questionnaire related to vaginal discharge. Of the women who did respond, only 6% complained of discharge, but 51% were found were found to have abnormal vaginal discharge on clinical examination (Marx et al., 2010). Another study, also in pregnant women, found that although many of the women questioned recognized a variety of symptoms (including vaginal discharge/itching, dysuria, and genital ulcers or swelling) only 9% sought treatment (Blankhart et al., 1999). This statistic is particularly disturbing in view of the adverse outcomes associated with having an STI during pregnancy. Reluctance to seek STI treatment for fear of negative reactions from family and/or community is putting both child and maternal health at risk.

5.2.3 Sexual inequality and risk

Sexual risk behaviour in women has been found to significantly influence their likelihood of contracting trichomoniasis, but not HIV. Conversely high risk (male) partner behaviour significantly increased the female partner's risk of acquiring HIV, but was not associated with increased incidence of trichomoniasis (Mavedzenge et al., 2010). This issue of male sexual risk behaviour contributing to a female partner's risk of acquiring an STI, especially HIV, is important because many women do not have complete control of their sexual activities. A study of 481 pregnant young women in the Central African Republic showed that 72% reported voluntarily engaging in their first sexual intercourse, 18% were pressured their first intercourse, and 11% reported their first sexual intercourse was a rape. With respect to their pregnancies, 52% reported their pregnancy was planned and desired, 32% reported unplanned but accepted, and 16% reported that they did not desire the pregnancy (Blankhart et al., 1999).

A study on risk factors for HIV acquisition in Africa found that women's sexual choices are often limited or dictated by their male partners. Some women reported that they were

forced into a sexual relationship as it was their only means to obtain food, shelter, or money for education. Others stated that they required their partner's permission to obtain medical care (including HIV testing) and to protect themselves (ie. use condoms). Marital standards are also unbalanced as while married women are expected to remain faithful to their husbands, men are not necessarily expected to maintain complete fidelity, especially if they are away from their wives (Chersich & Rees, 2008).

In many rural areas labourers must migrate to different locations or into cities to find work. This can result in significant periods of spousal separation and can result in one or both partners seeking extra-marital sexual intercourse. A study in Zimbabwe showed that while both partners may visit "beer halls" women are at statistically significant increased risk of HIV acquisition, while only a small non-significant increase in risk was seen for men (Gregson et al., 2001). In China, a study of migrant workers of both sexes found that they often engaged high risk sexual behaviours much more than the general population. In particular women were more likely to sell sex for money and men more likely to pay for sex. Interestingly, this increased involvement with the sex trade increased the prevalence of STI and HIV in women, but no statistically significant increase seen in men (Wang et al., 2007).

5.2.4 Marginalized populations

Female sex workers (FSW) are unsurprisingly at a high risk for STI. They can also act as a reservoir for STI that can be difficult to deal with using treatment alone as they can be sexually active on a daily basis. Additionally studies like one in Indonesia have shown that STI rates are highest in FSW in the lowest socioecomonic class, who charge the lowest prices per sex act and as such need to see more clients, increasing their risk for STI. These women are also more likely to have little ability to negotiate condom use, and have minimal money to spend on medical care and medication (Joesoef et al., 1997).

Even when healthcare initiatives aimed at FSW are in place, education and medical care are still not necessarily easily available to all. This is especially true for FSW who are non-residents or illegal immigrants in the country in which they are working. A study in Sydney, Australia showed an impressively low rate of STI amongst "local" FSW (women who were native Australian or had been in the country a significant period, and English-speaking) after partial legalization of the sex trade and an aggressive education campaign. However "international" FSW (women born outside of Australia whose first language was not English) showed high rates of STI. Language barriers, lack of access to the same medical programs as residents, and concerns about drawing attention to themselves by accessing medical care meant that these women remained at high risk despite there being a system in place to help protect them (O'Connor et al., 1996).

Sex trade workers are clearly an excellent target population for a vaccine that could provide long term, consistent protection from *T. vaginalis* infection and offer a reduced risk of HIV acquisition. They are part of a "core" group that acts as a reservoir for STI, and reducing the burden of infection in this population can be a community benefit.

5.3 Advantages of a vaccine for prevention of *T. vaginalis* infection

Trichomoniasis can be treated relatively easily and inexpensively, yet the disease is poorly controlled. Diverse factors lead to both a failure to recognize *T. vaginalis* infection and inability or unwillingness to seek or access treatment. A vaccine could provide long term protection eliminating the need for repeated doctor visits and treatments, the risk of

misdiagnosis, and address the needs of high risk populations. In addition, given the link between trichomoniasis and other genital infection, especially HIV, a vaccine capable of preventing *T. vaginalis* infections has the potential to impact global STI burden.

6. *T. vaginalis* and HIV

6.1 Incidence and prevalence of trichomoniasis and HIV

It is estimated that approximately 33.3 million people are currently infected with HIV-1. About two-thirds of these (22.5 million) are living in sub-Saharan Africa and 4.1 million live in South and Southeast Asia (UN, 2009). Both these areas also have the highest rates of *T. vaginalis* infection, with about 32 million cases in sub-Saharan Africa and 76.5 million in South and Southeast Asia every year (WHO, 2001). Global rates of trichomoniasis and HIV tend to follow similar patterns in different areas of the world (ie. the higher the incidence of *T. vaginalis* infection, the higher the prevalence of HIV) with two exceptions. As stated above, sub-Saharan Africa has the highest prevalence of HIV and the second highest incidence of trichomoniasis, while the opposite is true for south and Southeast Asia. The other exception is North America, which has a fairly high prevalence of HIV (1.5 million cases) (UN, 2009) relative to a low incidence of *T. vaginalis* infection (8 million annually) (WHO, 2001).

Rates of co-infection with HIV and *T. vaginalis* in women have been reported to range from 16% to almost 30% (Allsworth et al., 2009; Gatski et al., 2010; Månsson et al., 2010; Marx et al., 2010). It is difficult to reliably estimate co-infection rates in men as trichomoniasis is generally asymptomatic and not usually considered a significant STI in males.

6.2 *T. vaginalis* and increased risk of HIV transmission

Trichomoniasis has been associated with a 1.52 to 2.05 times greater risk of seroconversion upon exposure to HIV (McClelland et al., 2007, Mavedzenge et al., 2010). A longitudinal study of almost 5000 women in South Africa and Zimbabwe showed that the link between HIV and *T. vaginalis* appears to be bi-directional. Compared to uninfected women, those with trichomoniasis were more likely to test positive for HIV at their next study visit, and HIV positive women were more likely to have acquired *T. vaginalis* infection by their following study visit (odds ratios were >2 for both cases, after adjusting for confounders such as age, other STIs, and sexual risk behaviours) (Mavedzenge et al., 2010). This leads to an increased risk of both *T. vaginalis* and HIV infection if both diseases are present in any combination between sexual partners.

6.2.1 Disruption of genital mucosa

As previously mentioned, *T. vaginalis* is capable of both contact dependent and contact independent disruption of cell layers (see section 2.5.2). This disruption can provide portals of entry that allow HIV access past the epithelium into tissue, can sometimes lead to the formation of punctuate mucosal hemorrhages (strawberry cervix) women.

Without co-factors such as STI co-infection or trauma to the genital mucosa, the odds of a woman acquiring HIV through sexual exposure are estimated to be 0.08%. The odds of female to male transmission are 0.04% per exposure. Healthy, intact genital mucosa is considered to be a significant barrier to HIV infection (Thurman & Doncel, 2011). Because trichomoniasis can disrupt the integrity of mucosal tissue this primary barrier against infection is breached and HIV transmission risk is increased.

The degree of epithelial disruption has been found in vitro to vary between different isolates of *T. vaginalis*. A study examining four different *T. vaginalis* clinical isolates (two from asymptomatic patients and two from symptomatic patients presenting with cervicitis and vaginal discharge) found that the symptomatic isolates rapidly disrupted cell monolayers, but the asymptomatic isolates had a much more limited effect on monolayer integrity. The potential impact of monolayer disruption on the ability of HIV to enter tissue was examined by adding HIV and *T. vaginalis* to the apical surface of stratified monolayers growing on transwell plates, then measuring the amount of virus present in the basolateral supernatant. The degree of monolayer disruption was found to correlate with the amount of HIV released into the basolateral supernatant. Symptomatic isolates (disrupted monolayers) caused a four- to five-fold increase in HIV released into supernatant, whereas asymptomatic isolates (intact monolayers) showed HIV supernatant levels similar to background (no trichomonads on monolayers) (Guenthner et al., 2005). Although only four isolates were used, this experiment suggests that not all isolates of *T. vaginalis* may have equal impact on the risk of acquiring HIV infection. This is an intriguing possibility that could potentially offer some explanation as to why the high incidence of trichomoniasis in South and Southeast Asia is not matched by an equally high prevalence of HIV.

6.2.2 Changes to vaginal flora

Both trichomoniasis and HIV transmission have been linked to disrupted or abnormal vaginal flora. A study examining the link between *T. vaginalis* infection and bacterial vaginosis (BV) showed that 61% of HIV positive women also had BV and 80% had abnormal vaginal flora (defined as Nugent scores of 7-10 and 4-10, respectively). In comparison HIV negative women with trichomoniasis showed 47.3% incidence of BV co-infection, and 58.9% had abnormal vaginal flora (Gatski et al., 2010). However, since co-infection with trichomoniasis and BV is relatively common, it is difficult to tell which, if either, infection acts as the primary risk factor.

Both trichomoniasis and BV are associated with an increase in vaginal pH and decreased or absent vaginal *Lactobacillus* species (Petrin et al., 1998 (trichomoniasis) and Sha et al., 2005 (BV)). Lactobacilli produce lactic acid which maintains the low pH of the (healthy) vagina. Lactic acid has been shown in vitro to inactivate HIV, as has H_2O_2 which is produced by some, but not all, lactobacilli (Klebanoff et al., 1991). Lactobacilli therefore contribute maintaining a vaginal milieu that is not permissive to infectious agents, and loss of *Lactobacillus* species can lead to increased chances of STI. Low vaginal pH and H_2O_2 can also inhibit activation and proliferation of vaginal lymphocytes, particularly CD4+ T cells (Hill & Anderson, 1992). This means that disruption of the vaginal environment by *T. vaginalis* can lead to greater risk of HIV infection due to an increase of activated CD4+ T cells that can be infected by the virus.

6.2.3 Inflammatory response

Infection with *T. vaginalis* leads to a local inflammatory response that includes chemoattractant (IL-8) and acute pro-inflammatory (TNF-α ,IL-1β, and IL-6) cytokines that are responsible for initiating immune response to infection and recruiting immune cells. Symptomatic infection is the result of a more vigorous immune response in which there is an increased amount of inflammation and cell recruitment. For example, in women vaginal discharge often contains neutrophils that respond to the presence of IL-8 (Thurman & Doncel, 2010). However immune response may fail to clear *T. vaginalis*, and does not

provide long term immunological memory to prevent subsequent infections. Additionally immune response to trichomoniasis can attract lymphocytes that are the targets of HIV infection.

A powerful chemoattractant, IL-8 recruits immune cells to where they are needed to eliminate infection. However, it has also been shown that this cytokine can increase the susceptibility of monocytes, macrophages, and CD4+ T cells to HIV infection. IL-8 can also enhance HIV replication in infected immune cells (Narimatsu et al., 2005).

A study using cervicovaginal lavage samples from HIV positive women who were also infected with *T. vaginalis* showed elevated levels of IL-1β. Levels of IL-1β could be significantly different between visits, but clearly correlated with HIV viral load (Mitchell et al., 2011).

An in vitro study using HIV-infected peripheral blood mononuclear cells (PBMC) cultured with *T. vaginalis* resulted in increased replication of HIV compared to PBMCs alone. Unlike epithelial cell disruption, different isolates (symptomatic or asymptomatic) seemed to induce similar levels of increase in HIV replication. It was found that TNF-α levels were elevated in the supernatant of cultures containing *T. vaginalis* compared to controls and the addition of anti-TNF-α antibody could attenuate the increase in HIV replication (Guenthner et al., 2005).

The relationship between IL-6 and HIV is interesting in that they seem to be capable of upregulating each other in an apparent positive feedback loop. Examination of ectocervical tissue from HIV positive women found higher levels of IL-6 than in uninfected controls. Because the ectocervix was an area where high levels of HIV replication had been detected, recombinant IL-6 was applied to tissue explants and a greater than 300-fold increase in HIV transcription was seen (Asin et al., 2009). HIV appears to be capable of not only infecting immune cells, but of using immune response to its own advantage to enhance its replication.

6.2.4 Increased viral load

Inflammatory response to *T. vaginalis* infection leads to an influx of susceptible lymphocytes and the release of cytokines that can upregulate the rate of HIV replication. This in turn can increase HIV viral load and lead to a higher risk of spreading the infection to unprotected partners. A study looking at HIV positive men with genital ulcers found HIV RNA increased in ulcers caused by herpes simplex virus type 2 (HSV-2) only if HSV-2 was present in the ulcer. However, co-infection with *T. vaginalis* increased HIV viral load in ulcers regardless of the presence of HSV-2 indicating that trichomoniasis leads to increased shedding of HIV regardless of (or perhaps even in synergy with) other STI (Paz-Bailey et al., 2010).

While trichomoniasis does increase the amount of HIV viral shedding, elimination of *T. vaginalis* infection returns HIV RNA levels in the genitals to lower levels. A study in Africa of HIV positive women with trichomoniasis measured viral RNA at the time of trichomonal infection, and then 2 weeks later after treatment when infection had been resolved. There was a 4.2 fold decrease in the amount of HIV shed (Wang et al., 2001). Another study in New Orleans examined vaginal viral shedding in HIV positive women with and without trichomoniasis. Women with *T. vaginalis* infection were almost twice as likely as women without trichomoniasis to have detectable HIV RNA in their vaginal secretions at baseline (36.2% vs 19.6%). One month following successful treatment for trichomoniasis, the number of women shedding HIV was reduced (although it remained significantly higher than in women previously uninfected by *T. vaginalis*). At followup visits three months after initial

interviews there was no significant difference in the number of women shedding vaginal HIV between the two groups (Kissinger et al., 2009), indicating that elimination of the parasite removes the enhanced HIV risks associated with trichomoniasis. As *T. vaginalis* clearly has a significant impact on HIV infection, reducing incidence of trichomoniasis has the potential to help control the incidence and prevalence of HIV.

6.3 Reducing *T. vaginalis* as a method of HIV prevention

Trichomoniasis is clearly associated with HIV risk, the question is can reducing *T. vaginalis* infections have an impact on the incidence of HIV? A study in Tanzania showed that a decrease in HIV prevalence in women was accompanied by a significant decrease in multiple STI, particularly trichomoniasis which dropped from 21.2% to 5% incidence over the 3-5 year cross-sectional study. This reduction in disease burden was attributed mainly to changes in sexual behaviour as a result of a multi-pronged sexual health awareness campaign. Interestingly very little change was seen in condom use or age of first sexual intercourse, but a dramatic decline was seen in women reporting having engaged in casual sex (Msuya et al., 2007). As a women's sexual risk behaviour is correlated with the risk of trichomonal infection, this study suggests that protecting women from *T. vaginalis* could contribute to protecting them from HIV. Since treatment has proved to be an ineffective method of reducing trichomoniasis, a vaccine could provide long term for protection to those who are both most at risk and least able to protect themselves.

A vaccine would also be helpful in targeting specific at risk populations. For example, black women have consistently been shown to have a higher incidence of trichomoniasis than women of other races (Shafir et al., 2009). This may be the result of sample bias, as many studies take place in inner-city clinics and in sub-Saharan Africa where other risk factors such as poverty and lack of education are also present. It could also be the result of certain common practices (eg. vaginal cleaning/douching), unknown biological factors, or a combination of factors that act synergistically to increase susceptibility to *T. vaginalis* infection. The availability of a vaccine could target protection to those with increased risk, while avoiding stigmatizing a specific population. As this population has also been found to have an increased risk of HIV infection, an single effective vaccine could potentially have a significant impact on the incidence of both diseases.

HIV and the spectrum of medical issues that arise from infection are complicated issues that are often not well understood by either the HIV positive or the HIV negative. For example, many people believe if an HIV-positive person has an undetectable viral load, that they cannot infect anyone else. However, it has been shown that up to 33% of women with undetectable serum viral load continue to shed the virus in cervicovaginal secretions (Neely et al., 2007). Due to high rates of co-infection with *T. vaginalis* it is likely that a number of these women have or will acquire trichomoniasis. A *T. vaginalis* vaccine could reduce the burden of disease in HIV positive individuals who are at high risk to acquire trichomoniasis, and protect their partners from the elevated risk associated with co-infection.

7. Conclusions

Current methods for reducing the incidence of HIV include education and public health programs (providing condoms and encouraging condom use, needle exchange, etc.) and antiretorviral therapy (ART) to reduce HIV viral titers and minimize the risk of transmission. However, HIV is endemic in developing countries where obtaining resources

(financial, personal, etc.) and accessing (may need to travel from rural areas to cities) education and health programs can be difficult, potentially limiting positive impact. Providing ART also poses a problem in resource limited settings as it is an expensive multi-drug cocktail and therapy is often complicated by drug interactions and toxicity, and adverse patient reactions. Additionally, ART is usually prescribed based on CD4+ T cell count, and monitoring can be difficult if patients must travel to reach a medical facility capable of testing (WHO, 2006). Finding simple, inexpensive alternative methods to reduce the transmission of HIV could help reduce dependence on ART as a means of controlling HIV incidence.

Treatment of STI can be difficult for reasons beyond drug availability and efficacy and access to healthcare. Cultural barriers and personal beliefs can affect an individual's acceptance of their diagnosis and willingness to seek treatment. Limited control over one's sexual activity can lead to an inability to protect oneself and control sexual risk. In addition, some populations (eg. FSW) are at a persistently higher risk for STI and while treatment eliminates disease, it does not protect against subsequent infection thus will have minimal impact on STI incidence. The development of a *T. vaginalis* vaccine that could be offered as part of routine medical care for high risk groups could eliminate the need to seek treatment, reduce risk, and lower the incidence of trichomoniasis.

T. vaginalis infection has been shown to facilitate both transmission and acquisition of HIV through multiple mechanisms. Many of these mechanisms have been described in vitro, but their exact correlation to infection is not clearly defined. The existence of a mouse model of *T. vaginalis* infection provides a powerful and relatively inexpensive tool to elucidate the disease mechanisms of trichomoniasis in vivo. The model also allows for the evaluation of immune responses to *T. vaginalis* infection and vaccination as a part of an approach to rational vaccine design.

The actual increase in risk of acquiring HIV or infecting a sexual partner due to trichomoniasis is unknown. However, given that the high incidence of *T. vaginalis* infection (174 million cases annually), the fact that it is globally distributed in similar patterns to those of HIV, and that some populations have been found to have co-infection rates as high as almost 30% (Allsworth et al., 2009), even a small percentage of *T. vaginalis* infections leading to seroconversion could significantly impact the incidence of HIV. Vaccination against *T. vaginalis* offered to "core" groups that act as reservoirs of STI could have the potential to reduce community incidence of both trichomoniasis and HIV. Pregnant women are also often at increased risk of trichomoniasis due to hormonal changes. Vaccinating against *T. vaginalis* would not only prevent adverse birth outcomes associated with trichomoniasis, but could potentially protect against an HIV infection that could lead to maternal-child transmission of the virus. Thus, we suggest vaccination against *T. vaginalis* as an alternative approach to HIV control as well as for prevention of this highly prevalent STI.

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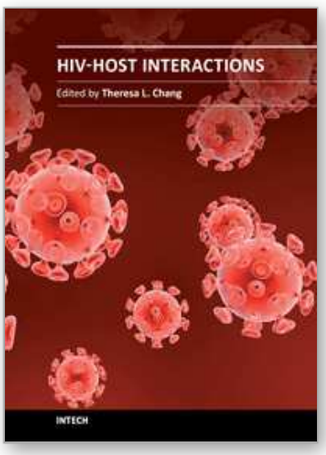

HIV-Host Interactions

Edited by Dr. Theresa Li-Yun Chang

ISBN 978-953-307-442-9
Hard cover, 364 pages
Publisher InTech
Published online 02, November, 2011
Published in print edition November, 2011

HIV remains the major global health threat, and neither vaccine nor cure is available. Increasing our knowledge on HIV infection will help overcome the challenge of HIV/AIDS. This book covers several aspects of HIV-host interactions in vitro and in vivo. The first section covers the interaction between cellular components and HIV proteins, Integrase, Tat, and Nef. It also discusses the clinical relevance of HIV superinfection. The next two chapters focus on the role of innate immunity including dendritic cells and defensins in HIV infection followed by the section on the impact of host factors on HIV pathogenesis. The section of co-infection includes the impact of Human herpesvirus 6 and Trichomonas vaginalis on HIV infection. The final section focuses on generation of HIV molecular clones that can be used in macaques and the potential use of cotton rats for HIV studies.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Sarah Cudmore, Jeffrey Smith and Gary Garber (2011). Inducing Immune Protection Against Trichomonas vaginalis: A Novel Vaccine Approach to Prevent HIV Transmission, HIV-Host Interactions, Dr. Theresa Li-Yun Chang (Ed.), ISBN: 978-953-307-442-9, InTech, Available from: http://www.intechopen.com/books/hiv-host-interactions/inducing-immune-protection-against-trichomonas-vaginalis-a-novel-vaccine-approach-to-prevent-hiv-tra

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