

# Reducing Urogenital Infections Including HIV in Sub-Saharan Africa - Can Probiotics Be a Viable Paradigm?

Kingsley C. Anukam<sup>1,2</sup>, Enya B. Bassey<sup>3</sup> and Emmanuel O. Osazuwa<sup>2</sup>

<sup>1</sup>*TWAS Research Unit on Probiotic Genomics, Department of Medical Laboratory Science, School of Basic Medical Sciences, College of Medical Sciences, University of Benin,*

<sup>2</sup>*Department of Pharmaceutical Microbiology, Faculty of Pharmacy, University of Benin,*

<sup>3</sup>*World Health Organization (WHO), Ministry of Health, Uyo, Akwa Ibom State, Nigeria*

## 1. Introduction

The economic burden, albeit low quality of life of people in sub-Saharan Africa with non-sexually transmitted recurrent urogenital tract infections is not the desired state of health. Associations exist between abnormal vaginal/penile microbiota and HIV. Excluding sexually transmitted diseases, microorganisms that originate from the gastrointestinal tract cause almost all infections of the vagina and bladder. There is a strong correlation between presence of the normal microbiota, particularly lactobacilli in the vagina with health, and an absence of these microorganisms in patients with urogenital infections. Disruption of the normal vaginal microbiota is caused by the use of broad-spectrum antibiotics, spermicides, hormones, dietary substances and factors not, as yet, fully understood. There is increasing body of evidence that probiotic microorganisms delivered in food such as yogurt or milk based foods and capsular preparations do have a role in preventing urogenital tract infections and in ameliorating diarrhea [Walker et al., 2006].

The use of probiotics defined as “live microorganisms which when administered in adequate amounts, confer health benefits on the host” (WHO/FAO, 2001), for the maintenance of health is already in use in developed countries. Probiotics are yet to be adopted in sub-Saharan Africa by health care providers. There are clinical evidence to show that probiotics can play a significant role in resolving diarrhea, boost immune system and prevent recurrent urogenital infections including bacterial vaginosis, which is a risk factor in HIV acquisition. The aim of this chapter is to highlight the burden of urogenital infections in Africa, impact of abnormal vaginal microbiota, clinical evidence on the use of probiotics for urogenital health care and last but not the least, the rationale for suggesting the use of probiotics in the management of HIV infection in sub-Saharan Africa.

## 2. Burden of urogenital infections in Africa

Non-sexually transmitted urogenital infections such as bacterial vaginosis (BV), yeast vaginitis, urinary tract infections (UTI) afflict more than one billion women around the world annually [Hay, 2000]. However, it is worthwhile to briefly explain what BV is.

BV is a syndrome defined by symptoms and signs of a white, homogenous, malodorous discharge, vaginal itching, increase in vaginal pH above 4.5, development of a fishy odor when 10% KOH reacts with an altered organic acid pattern (including increases in putrescine, cadaverine, and trimethylamine), and vaginal epithelial cells observed on wet mount spotted with adherent small rods or cocci ("clue cells"). Three of 4 (discharge, pH, odor, clue cells) clinical or laboratory signs are required for BV diagnosis by the Amsel criteria [Amsel et al., 1983]. The relative changes in bacterial concentrations have been tracked by Nugent scoring, which uses staining and microscopy to grade the predominance of 3 morphotypes: lactobacilli, small gram-variable rods or Gram-negative rods (*G. vaginalis*, *Bacteroides*), and curved gram-variable rods [Nugent et al 1991]. Currently, molecular techniques are providing new ways to categorize the change in composition of the vaginal microbiota [Verhelst et al 2005]. The predominance of *G. vaginalis*, *Bacteroides* spp., and *A. vaginae* in BV is also accompanied by increases in other anaerobes, such as prevotella, mobiluncus, genital mycoplasmas, and an unfolding community of unculturable bacteria but not necessarily a decrease in the geometric mean concentration of lactobacilli [Fredricks et al 2007]

Although the estimate for non-sexually transmitted urogenital infections in women in sub-Saharan Africa is difficult to get, but statistics may be grim due to the rising trend in HIV/AIDS in the region. The infection process is not a hygiene issue. Anatomically, the proximity of the vagina and the anus predisposes women to these infections. Most cases of BV, UTI, and yeast vaginitis arise from the host's gastrointestinal tract, as microbes ascend 4 to 5 cm from the anus, thereby showing that the intestine and urogenital tracts are 'connected' and that intestinal health can influence the vagina and bladder. The process is mediated by bacterial adherence and is not altered by antibiotic use. Studies have shown that the host's cells remain susceptible to pathogen adhesion before, during and after antibiotic administrations [Reid et al 1988]. Since the discovery of the 'magic bullet', the therapeutic approaches to treatment and prevention of urogenital infections in Africa and in the rest of the world have remained constant for more than half of a century. Antibiotics and antifungals still remain the armaments of therapy, despite their well-known side effects chronicled in Pharmaceutical compendia, ranging from super infections, diarrhea, depression, to renal failure. The emergence of 'superbugs' as a result of antimicrobial resistance is not only an economic burden to the health sector, but also constitute a treat to the survival of the human species.

The burden of urogenital infections is becoming more worrisome in that most women are not aware that they have particularly, bacterial vaginosis. Klebanoff et al [2004], recently revealed that women not detecting odor or discharge do not realize that their vaginal microbiota is abnormal and a 14.2% prevalence of BV have been found in healthy Nigerian women [Anukam et al 2006]. Consequently the quality of life of the women with these acute and chronic infections has been found to be adversely affected significantly [Ellis &Verma, 2000]. There is an association between BV and preterm delivery [Hay, 1994] and also between BV and early spontaneous miscarriage prior to 16 weeks gestation [Oakeshott et al., 2002]. Associations between BV and urinary tract infections (UTI) [Hillebrand et al., 2002] as well as between BV and history of infertility caused by tubal factors [Wilson et al., 2002] have been reported in other studies. There is also an association between smoking and BV [Smart et al., 2004].

A previous longitudinal study of women in the United Kingdom showed that at any given time during the menstrual cycle, the vaginal microbiota may be "abnormal" [Keane et al 1997]. When symptoms of pain, discharge, and itching occur, many women diagnose these

symptoms as yeast infections and self-treat with over-the-counter antifungals, when in fact they have BV. This misdiagnosis and mistreatment can result in adverse consequences [Ferris et al 1996]. Antimicrobial treatment for BV is suboptimal, with some cure rates as low as 60% 1 month after treatment, and subsequent overgrowth of pathogenic bacteria in the vagina often occurs [Livengood et al 1999].

### **3. Abnormal vaginal/penile microbiota and HIV**

Studies have found a significant association between BV and human immunodeficiency virus (HIV) infection (Sewankambo et al., 1997). In a prospective study of Kenyan sex workers, the absence of lactobacilli in vaginal cultures was associated with a 2.0-fold increase in HIV acquisition and a 1.7-fold greater risk of developing gonorrhea (Martin et al., 1999). Similar studies have also documented evidence indicating that human immunodeficiency virus infection have a strong association with abnormal vaginal microbiota particularly, bacterial vaginosis [Taha, 1999]. Studies have also shown that the absence or depletion of lactobacilli in the vagina associated with overgrowth of anaerobic pathogens causing BV results in significantly increased risk for HIV (as well as gonorrhea, chlamydia, and herpes simplex virus infections) [Wiesenfeld, 2003]. By mechanisms yet to be elucidated, BV displaces lactobacilli, elevating vaginal pH and creating an environment within which the pathogens survive and can infect the host. It is important to note also that penile microbiota may contribute significantly to susceptibility to HIV infection. Several randomized trials demonstrated decreased risk of trichomoniasis and bacterial vaginosis (BV) in the female sexual partners of circumcised men (Gray et al 2009). It is very pertinent to better understand the biological mechanisms by which male circumcision reduces the risk of HIV infection as this may lead to the development of novel, non-surgical prevention strategies. It has been asserted that male and female genital microbial communities may play an important role in modulating HIV risk [Galvin & Cohen, 2004]. Genital mucosal inflammation induced by microbes leads to the activation of HIV target cells and an increase in HIV susceptibility [de Jong & Geijtenbeek, 2009]. The dominant HIV target cells in the genital mucosa are two dendritic cell types, langerin+ Langerhans' cells and DC-SIGN+ dendritic cells. The biological mechanism underlying circumcision-conferred protection against HIV is likely to be multifactorial. Post-circumcision anatomical, immunological, and microbiological changes have all been hypothesized to contribute to the reduction in HIV risk. From the anatomical and immunological perspective, the inner surface of the foreskin is lightly keratinized and contains abundant Langerhans cells close to the mucosal surface resulting in a large number of exposed HIV target cells in the erect uncircumcised penis (Patterson et al., 2002; McCoombe & Short, 2006). From a microbiological perspective, the intact foreskin may support the survival of genital microbes associated with increased foreskin mucosal inflammation and Langerhans' cell activation. Of note, the protection against sexually transmitted infections and BV conferred to the female partners of circumcised men [Bailey et al., 2007; Auvert et al., 2005; Gray et al., 2009] strongly suggests circumcision-associated microbiological changes in the male genital mucosa.

In a study that assessed the penile (coronal sulci) microbiota in 12 HIV-negative Ugandan men before and after circumcision revealed a total of 42 unique bacterial families in the coronal sulci microbiota, with 38 bacterial families among pre-circumcision samples versus 36 detected among post-circumcision samples. Pseudomonadaceae was the most abundant family irrespective of circumcision status, constituting over 50% of the coronal sulci

microbiota, followed by Clostridiales Family XI, Oxalobacteraceae, and Prevotellaceae for pre-circumcision and Corynebacteriaceae, Oxalobacteraceae, and Staphylococcaceae for post-circumcision (Price et al 2010). The study suggests that anoxic microenvironment of the subpreputial space may support pro-inflammatory anaerobes that can activate Langerhans cells to present HIV to CD4 cells in draining lymph nodes. Thus, the reduction in putative anaerobic bacteria after circumcision may play a role in protection from HIV and other sexually transmitted diseases.

#### 4. The role of normal vaginal microbiota

It has been reported previously that more than 60 different bacterial species colonize the healthy vagina (Reid et al 1990). A recent study sampled the vaginal bacterial communities of 396 asymptomatic North American women who represented four ethnic groups (White, Black, Hispanic and Asian) and the species composition was characterized by pyrosequencing of barcoded 16S rRNA genes. The study revealed that the bacterial communities clustered into five groups: four were dominated by *Lactobacillus iners*, *L. crispatus*, *L. gasseri*, or *L. jensenii*, whereas the fifth had lower proportions of lactic acid bacteria and higher proportions of strictly anaerobic organisms, indicating that a potential key ecological function, the production of lactic acid, seems to be conserved in all communities. The proportions of each community group varied among the four ethnic groups, and these differences were statistically significant (Ravel et al. 2011). This shows that different vaginal bacterial ecosystems varies in people but conferring the same protective role as the human vaginal microbiota seem to play a key role in preventing a number of urogenital diseases, such as bacterial vaginosis, yeast infections, sexually transmitted infections, urinary tract infections and HIV infections (Taha, 1999). Studies have shown that urogenital cells are covered by dense bacterial biofilms, whose composition changes constantly, but in which lactobacilli predominate, at least until menopause. Vaginal lactobacilli have been shown to inhibit the growth of *Gardnerella vaginalis* and *Mobiluncus* in vitro, with the greatest inhibition observed in the presence of lactobacilli producing lactic acid. Hydrogen peroxide-producing lactobacilli have been recovered from the vagina of 96% of 28 non-pregnant women without bacterial vaginosis, compared with 6% of 67 women with bacterial vaginosis (Eschenbach et al. 1989). The presence of lactobacilli on vaginal epithelial cells seems to act, not only as a barrier to infection, by blocking adherence of pathogens, but their capability of producing such antibacterial materials as hydrogen peroxide to limit pathogen growth, production of biosurfactants that inhibit pathogen adherence, and their ability to prime macrophages, leukocytes, cytokines, and other host defenses also contribute to the protection of the vagina against uropathogens (Reid, 1999). Full genome sequencing of *Lactobacillus plantarum* KCA1 isolated from the vagina of a healthy Nigerian woman has revealed the presence of several novel phage defense genes encoding clustered regularly interspaced short palindromic repeats (CRISPR)-associated proteins and abortive infection systems (Anukam et al. 2011). One of the fastest evolving genetic elements in bacterial genomes are clustered regularly interspaced short palindromic repeats (CRISPRs) (Sorek et al., 2008). CRISPRs have been identified within the genomes of many archaeal and bacterial species especially in some vaginal lactobacilli such *L. plantarum* KCA-1, the only plantarum strain know to date with CRISPR. The Spacers are derived from foreign nucleic acids, such as those from phage or plasmids and can protect bacteria from subsequent infection by homologous phage and plasmids. As a bacterial immune system against foreign DNA,

CRISPRs evolve rapidly in response to changing phage pools (Vale & Little, 2010) that is usually encountered in the vaginal niche as a result of changes occasioned by the menstrual cycle.

## 5. The impact of HIV/AIDS in Africa

Recently, the United Nations AIDS program (UNAIDS) estimated that around 25 million people around the world have died from AIDS in the past 30 years since it was recognized, and about 40 million more are currently infected with the virus. It is astonishing that 14,000 new infections occur per day, which means that in every six seconds someone in the world will be infected with the HIV virus. Sub-Saharan Africa has been hit hardest by the pandemic: about 83% (18.26 million) of AIDS deaths and 71% (28.4million) of HIV infections have occurred in this war-ravaged, poverty stricken part of the continent probably due to political instability and global climate changes. African region holds just over 10% of the world's population, but is home to more than 60% of all people living with HIV and more than two-third of all women living with HIV. In some African nations, over 30% of the adult population is HIV-positive. (UNAIDS, 2002). In Nigeria, with about 25% of the African population, a recent national HIV prevalence sentinel survey by the Federal Ministry of health showed that the number of people living with HIV/AIDS in 2009 was between 3.2 and 3.8 million (Report, 2009). According to the report, the age group 20-24 years had the highest national prevalence of 5.6 per cent, and the HIV prevalence for women aged 15-24 years remains 5.2 per cent. The statistics are very grim all over Africa, in that in 2000, of the 1.4 million children world-wide living with HIV/AIDS, 1.1 million were in sub-Saharan Africa alone (Sengupta and Somini, 2002). By 2002, about 11 million children in Africa had lost one or both parents to AIDS. If the disease remains unchecked, the number of African children orphaned by AIDS will jump to 20 million by 2010 and most will be old enough to watch their parents die from the disease. (Altman and Lawrence, 2002).

In Africa alone, AIDS has surpassed armed conflict as the leading cause of death (Van Niekerk, 2001). With the increasing number of people living and dying of AIDS, only a few people have easy access to life-prolonging antiretroviral drug therapy. According to UNAIDS, in a press release in July 2, 2002 "In high-income countries, where an estimated 500,000 people were receiving antiretroviral treatment, 25,000 people died of AIDS in 2001. In Africa, however, where only 30,000 of the 28.4 million people infected, were receiving antiretroviral treatment, AIDS killed 2.2 million people". In Nigeria, if not for PEPFAR, the situation is harrowing in terms of provision of antiretroviral drugs to people living with HIV/AIDS. According to Dr. Peter Piot, executive director of UNAIDS, "The devastating impact of HIV/AIDS is rolling back decades of development progress in Africa, and has caused economic growth to plummet as much as 4% in sub-Saharan Africa". HIV/AIDS will prevent many sub-Saharan African countries from achieving the Millennium Development Goals (MDGs). In high-prevalence countries (those with more than 10% of adults infected: Botswana, Lesotho, Malawi, Mozambique, Namibia, South Africa, Swaziland, Swaziland, Zambia and Zimbabwe), AIDS is the leading cause of death (MSF, 2009).

Over 7,000 women become infected each day. In sub-Saharan Africa, around one quarter of females under the age of 30 have HIV and an estimated half billion are at risk of acquiring the virus through sexual contact. Although efforts to provide condoms, develop a vaccine, use spermicides or anti-retrovirals, have contributed significantly to stem the epidemic due

to massive investment by International organizations, such as the Joint United Nations Programme on HIV/AIDS (UNAIDS), the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund) and the US President's Emergency Plan for AIDS Relief (PEPFAR). These organizations were formed to specifically address HIV/AIDS. The United Nations estimated that at least US \$1.5 billion a year could make it possible to achieve massively higher levels of implementation of all major components of successful prevention programs for the whole of sub-Saharan Africa.

Having HIV/AIDS is especially devastating among children from the developing countries such as sub-Saharan Africa. To comprehend the reality of the vulnerability of children affected by the condition, it is important that health care professionals and national policy makers understand the global magnitude of the problem. More than 90% of HIV infection occurs among the children of southern Africa. Seventy-five percent of those children reportedly die before the age of 5 years (DeBaets et al., 2007). Children with HIV/AIDS in developing countries continue to be underrepresented among recipients of antiretroviral therapy or supportive care, including palliative care (Kline, 2006). A significant number of children infected with HIV are also orphans of parents who died of HIV, and they suffer from complications including extreme malnutrition. Children who receive professional care are often hospitalized for many months at the end of life. The need for prevention and alternative management is very obvious

Meanwhile, more than half of those in need still do not have access to treatment, and treatment is posing new challenges for sustainable funding. Most countries with mid to high prevalence cannot afford the cost of treatment without international aid; as aid is reduced or cancelled, treatment programmes are threatened, drug resistance develops and large numbers of people living with HIV may die. In countries like Uganda, patients are being turned away from treatment clinics due to lack of resources; 300,000 Ugandans in need of treatment are denied their right to health (McNeil, 2010). These numbers will continue to grow if both effective prevention and sustainably funded treatment programmes are not maintained. Nigeria may not be able to sustain the free anti-retroviral drug program from PEPFAR and the future of new infected person may be grim. In 2009, UNAIDS and WHO predicted that the \$25.1 million needed for HIV/AIDS programmes in 2010 would not be forthcoming (UNAIDS, 2009). The total amount of Global Fund grants recommended for funding in 2009 was 35% lower than in 2008 (MSF, 2009).

The programs by all these agencies are planned to cover sexual, mother-to-child and transfusion-related HIV transmissions, and would involve approaches ranging from awareness campaigns through media to voluntary HIV counseling and testing and the promotion and supply of condoms.

No doubt these programs are laudable, but other alternative measures, such as nutrition fortification and probiotics, have not been included as one of the UNAIDS intervention programs. Death from AIDS is often precipitated by gastrointestinal infections and diarrhea, and indeed, many non-AIDS deaths are due to these infections. It has been estimated that a child dies every 15 seconds from diarrheal diseases. While sanitation and early hydration based interventions can reduce this death rate, probiotics too could play a role.

## **6. Probiotics with clinical evidence against urogenital infections**

During the early periods of probiotics, Scientists paid more attention to gastrointestinal effects, but in recent times probiotics are now useful for more than just gastrointestinal

health. In fact, there are specific probiotic products that can help prevent and treat female urogenital conditions like bacterial vaginosis, vulvovaginal candidiasis, urinary tract infections. It should be noted that the vaginal tract is not internally connected to the alimentary canal, however the two are intimately related. Bacteria that pass through the digestive system can ascend via the perineum to the vagina. So it's almost a no-brainer to expect what promotes gastrointestinal health to have relevance for urogenital health.

In the late 1980s, human studies were carried out in which *L. rhamnosus* GR-1 in a douche suspension was instilled into the vagina (Bruce and Reid, 1988). This was followed by studies using a gelatin capsule containing freeze-dried lactobacilli inserted into the vagina (Reid et al 2001). In both cases, the process did not result in any adverse events but did show a potential to reduce the risk of recurrence of UTI. The use of orally administered lactobacilli was more recently tested, on the basis that if pathogens infect the host from the anal skin, why couldn't lactobacilli also ascend from the anus to the vagina and repopulate the area? This concept was verified in several labs (Reid et al, 2001; Antonio et al 2005), and *Lactobacillus* strains GR-1 and RC-14 were shown to reduce UTI, BV and yeast pathogens as well as infections (Reid et al 2001; Reid et al. 2003]. The mechanism of action is likely multifactorial and could include the ingested lactobacilli ascending from the rectal skin to the vagina, or causing a reduced pathogen ascension, or influencing the immune or host system in a way that reduces infectivity.

As this approach to restoration and maintenance of women's health has become more recognized, other groups have undertaken studies using different strains. A prospective clinical pilot study was performed to confirm the safety and effectiveness of *Lactobacillus* vaginal suppositories against the recurrence of UTI. The patients enrolled in the study were instructed to administer vaginal suppositories containing the strain *L. crispatus* GAI 98322. A significant reduction in the number of recurrences was noted, without any adverse complication ( $P=0.0007$ ). The administration of vaginal suppositories containing *L. crispatus* GAI 98332 seemed to be a safe and promising treatment for the prevention of recurrent UTI (Uehara 2006). Delai et al., (2006) demonstrated the effectiveness of the contemporary oral administration of *L. paracasei* subsp *paracasei* F19 in association with vaginal suppositories containing an unnamed *L. acidophilus* in the treatment of BV. The study had a potentially fatal flaw in that not all the 60 subjects had confirmed diagnosis of BV. The subjects were randomized in 2 groups: Group A treated with vaginal suppositories containing *L. acidophilus*; Group B treated with the same vaginal suppositories + *L. paracasei* subsp *paracasei* F 19 for oral administration. There was a significant reduction of vaginal pH, an improvement in the amine sniff test and in subjective symptomatology after 3 months of treatment and follow-up (3 months). This study needs to be repeated with larger sample size, but nevertheless, reviews of the evidence from microbiological and clinical studies have indicated that probiotics can be beneficial for preventing recurrent UTI in women in a safe manner (Falagas 2006; Reid and Bruce 2006; Hoesl and Altwein 2005).

The usefulness of orally administered lactobacilli for urogenital health has been demonstrated in several other important studies. In a randomized, double-blind, placebo controlled trial, 106 women with BV were given a single oral dose of metronidazole (500mg) twice daily from days 1-7, plus oral *L. rhamnosus* GR-1 and *L. reuteri* RC-14 or placebo twice daily from days 1-30. The cure rate in the antibiotic/probiotic group was 88% compared to 40% in the antibiotic/placebo group ( $p<0.001$ ). High counts of *Lactobacillus* sp.

(>10<sup>5</sup>CFU/ml) were recovered from the vagina of 96% of probiotic treated subjects compared to 53% controls at day 30 (Anukam et al 2006a). In another study using the same probiotics, there was a 90% cure of BV following intravaginal administration of the probiotic alone, compared to 33% cure with intravaginal metronidazole treatment. In the study, 40 women diagnosed with BV were randomized to receive either two dried capsules containing *L. rhamnosus* GR-1 and *L. reuteri* RC-14 each night for five days, or 0.75% metronidazole gel, applied vaginally twice a day (in the morning and evening). Follow-up at day 6, 15 and 30 showed cure of BV in significantly more probiotic treated subjects (16, 17 and 18/20 respectively) compared to metronidazole treatment (9, 9 and 11/20: P= 0.016 at day 6, P= 0.002 at day 15 and P= 0.056 at day 30) [Anukam et al 2006b]. This is the first proven cure of BV using probiotics and provides hope that alternative remedies to antibiotics can be found.

## 7. Mechanisms of action

Probiotics apparently fulfills the definition as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" through a variety of somewhat disparate, somewhat overlapping mechanisms. These include the regulation of intestinal microbial homeostasis, the interference with the ability of pathogens to colonize and infect the mucosa, the modulation of local and systemic immune responses, the stabilization or maintenance of the gastrointestinal barrier function, the inhibition of procarcinogenic enzymatic activity and the induction of enzymatic activity that favors good nutrition. For example, with respect to epithelial barrier function, probiotics can conceivably act through general antimicrobial effects, effects on intestinal permeability in the absence of invasive bacteria, effects on epithelial cell inflammatory responses and effects on epithelial cell survival. One important effect of probiotics on barrier function is the ability of commensal organisms to act through Toll-like Receptors (TLR) on epithelial cells (such as TLR2 and TLR4). In particular, it has been shown that such interactions induce the production of protective cytokines such as IL-6 that mediate epithelial cell regeneration and inhibit epithelial cell apoptosis in the face of agents that otherwise result in epithelial cell ulceration (Rakoff-Nahoum et al., 2004). It should be noted, however, that probiotics do not affect expression of all TLRs in the same manner. Thus, as shown by Ewaschuk *et al.*, (2007) whereas exposure of HT-29 epithelial cells to DNA from pathogenic organisms resulted in increased TLR9 expression, exposure to a probiotic did not have this effect. This is in keeping with the lesser ability of commensal organisms to induce TLR expression as compared with pathogenic organisms. Probiotics may also have effects on epithelial barrier function via cellular mechanisms that have little to do with TLR signaling. Thus, in a study by Zyrek *et al.*, (2007) it was shown that the probiotic, *E. coli* Nissle 1917 (EcN) counteracts the disruptive effects of enteropathic *E. coli* (EPEC) on T-84 epithelial cell monolayers by altering protein kinase C signaling and causing the redistribution and increased expression of zonula-occludens-2 (ZO-2), an important factor in maintaining epithelial tight junction function. Along similar lines, Yan *et al.*, (2007) showed that proteins isolated from broths of the probiotic *Lactobacillus rhamnosus* activated mouse epithelial cell Akt and inhibited TNF- $\alpha$ -mediated apoptosis and promoted growth of both human and mouse colon epithelial cells or cultured mouse colon explants.



Production of antimicrobial substances, such as organic acids or bacteriocins
Upregulate immune response (eg, secretory IgA) to possible pathogens or to vaccines
Downregulate inflammatory response
Assist in early programming of the immune system to result in a better balanced immune response and reducing risk of development of allergy
Improvement of gut mucosal barrier function
Enhance stability or promote recovery of commensal microbiota when perturbed
Modulate host gene expression
Deliver functional proteins (eg, lactase) or enzymes (natural and cloned)
Decrease pathogen adhesion

Table 1. Some proposed probiotics mechanisms of actions

From the accumulated information on the relation of regulatory T cells and their associated cytokines to the function of probiotics, it can be said with some certainty that probiotic administration does lead to the increased elaboration of regulatory cytokines and these cytokines play a major role in the protective effect of the probiotics. It seems likely that probiotics bring about these effects via their interactions with mucosal dendritic cells which then produce regulatory cytokines themselves or induce T cells with these properties. There is the possibility that probiotics act through the induction of regulatory T cells that suppress inflammation-inducing effector cells. This emphasis is based on a rising tide of evidence that probiotics have properties that allow them to interact with the mucosal immune system that does not arouse an inflammation inducing innate response and the consequent induction of master inflammatory cytokines such as IL-12. For example human circulating dendritic cells or lamina propria mononuclear cell populations were cultured with cell wall preparations from each of the probiotic species in VSL#3 and then assessed cytokine production. It was found that bifidobacteria components were generally the most potent in up-regulating IL-10 by both CD11+ and CD11- dendritic cells whereas components of all VSL#3 strains decreased IL-12 production (Mohamadzadeh et al., 2005). While studies on vaginal lactobacilli with respect to their probiotic potential are increasing, significant basic research studies have only been performed on strains GR-1 and RC-14, particularly looking at modes of action. It is clear that these organisms are multifunctional and may affect each host differently. The GR-1 strain does not produce hydrogen peroxide but does produce anti-candida activity as well as bacteriocins and other components, including AI-2 inducers that influence the growth and biofilm development of uropathogens. The organism can down-regulate inflammatory processes, using IL-10 dependent and independent pathways, as shown in macrophages studies (Kim et al. 2006). A human genome array study has shown that a single intravaginal insertion of *Lactobacillus* GR-1 can up-regulate host defense factors known to be important in fighting infection (Kirjavainen et al., 2008 ). Meanwhile, studies with *Lactobacillus* RC-14 strain have shown that it can up-regulate mucin production which may act as a barrier to infection (unpublished data), and down-regulate virulence factor expression in pathogens such as staphylococci [Laughton et al 2006]. The organism also affects cell membrane components in *E. coli* and produces biosurfactants that inhibit their adhesion to surfaces.

## 8. The rationale for the use probiotics in reducing the risk associated with HIV

Tremendous efforts are being made to develop effective microbicides for the prevention of HIV-1 sexual transmission and in clear terms it should represent a primary goal for the control of AIDS epidemics worldwide. A promising strategy is the use of bacteria belonging to the vaginal microbiota as live microbicides for the topical production of HIV-1 inhibitors. A recent review has chronicled the potentials of probiotics to prevent HIV (Bolton et al., 2008) and some of the points are lighted in line with the objectives of this section. A study engineered a human vaginal isolate of *Lactobacillus jensenii* to secrete the anti-HIV-1 chemokine RANTES, as well as C1C5 RANTES, a mutated analogue that acts as a CCR5 antagonist and therefore is devoid of proinflammatory activity. Full-length wild-type RANTES and C1C5 RANTES secreted by *L. jensenii* were purified to homogeneity and shown to adopt a correctly folded conformation. Both RANTES variants were shown to inhibit HIV-1 infection in CD4<sup>+</sup> T cells and macrophages, displaying strong activity against HIV-1 isolates of different genetic subtypes. The work provides proof of principle for the use of some Lactobacilli, notably *L. jensenii*-produced C1C5 RANTES to block HIV-1 infection of CD4<sup>+</sup> T cells and macrophages, setting the basis for the development of a live anti-HIV-1 microbicide targeting CCR5 in an antagonistic manner [Luca et al 2010]

Other studies have previously used Lactobacilli and other probiotic genetically modified bacteria to produce specific HIV inhibitory proteins, both membrane-bound and secreted. A strain of *L. jensenii* was engineered to produce functional CD4, the primary receptor for HIV [Chang et al, 2003]. There are several classes of proteins that bind to the mannose residues of HIV, including a unique 11 kd protein from cyanobacteria (*Nostoc ellipsosporum*) called cyanovirin-N and mannose-binding lectins which also bind to *Neisseria gonorrhoeae* [Botos & Wlodawer, 2005]. The human commensal bacterium *Streptococcus gordonii*, *L. lactis*, *L. plantarum*, and *L. jensenii* have been genetically engineered to express functional, HIV-binding cyanovirin-N [Pusch et al 2005; Liu et al 2006]. An *E. coli* strain which colonizes the colon and rectum, and may thus potentially prevent anal transmission, has been modified to secrete peptides hybridized with hemolysin A, a protein that can complex with the HIV fusion protein gp41 [Rao et al 2005]. FI-1, FI-2, and FI-3 are also peptides that can interfere with gp41 and were cloned into *L. plantarum* and *L. gasseri* [Pusch et al 2006]. *L. reuteri* RC-14, which has been studied as a potential probiotic, was modified to produce 3 HIV entry and fusion inhibitors: CD4D1D2IgKLC, MIP-1 $\alpha$ , and T-1249 [Liu et al 2006]. Antibody to the cellular adhesion molecule intercellular adhesion molecule has been shown to inhibit cell-mediated trans-epithelial HIV-1 transmission in vitro and was functionally excreted by a bioengineered strain of *L. casei* [Chancey et al 2006]. Some of these products have been used in rodent models, but none has been tested in humans.

By their production of lactic acid, lactobacilli may help maintain a low vaginal pH that can inhibit other bacteria and viruses. Among postmenopausal women receiving estrogen replacement therapy, those who were lactobacilli-positive had low pH 4.4 compared with the lactobacilli-negative women pH 5.2 (Ginkel et al 1993). In 55 menarchal women, colonization with hemolytic streptococci, *G. vaginalis*, or mixed organisms was associated with higher vaginal pH than colonization with normal microbiota and yeast (Caillouette et al. 1997). As previously mentioned, BV is associated with a lack of hydrogen peroxide-producing lactobacilli. Colonization with hydrogen peroxide producers is associated with lower frequency of gonorrhea (Antonio et al 1999). Compared with women colonized with

hydrogen peroxide-producing lactobacilli, women colonized with hydrogen peroxide nonproducers or without lactobacilli had unadjusted odds ratios of HSV-2 seroconversion of 2.4 and 2.6, respectively (Cherpes et al 2003). The difference in seroconversion rates may be due to a direct antiviral effect of hydrogen peroxide or due to an increased risk of HSV infection in women with BV.

Several mammalian peroxidases, including myeloperoxidase, eosinophil peroxidase, and lactoperoxidase can combine with hydrogen peroxide and a halide (chloride, iodide, bromide, thiocyanate) to form "a powerful antimicrobial system" effective against many pathogens (Klebanoff et al 1991). Lactobacilli, streptococci, and pneumococci can release hydrogen peroxide and in vitro, in mixed cultures, their toxicity against other bacteria, fungi, viruses, spermatozoa, and tumor cells can be boosted by addition of a peroxidase and a halide. This system was found to inhibit cell-free HIV replication in culture in the presence of hydrogen peroxide-producing, but not nonproducing, lactobacilli (Klebanoff et al 1991a, Klebanoff et al 1991b). *L. crispatus* and *L. jensenii* inhibit gonococci at both acidic and neutral pH. This inhibition is susceptible to bovine catalase, suggesting that hydrogen peroxide is the primary mediator (St Amant et al 2002). Lactobacilli have been found to produce many other bacteriocins, enzymes, and antimicrobial peptides that may make them more competitive in the vaginal microbiota (Silva et al 1987; Naidu et al 1999).

Another potentially beneficial characteristic of probiotic bacteria studied in the gastrointestinal tract is their pleomorphic effect on host mucosal immunity that could affect the vaginal mucosa's defense against HIV and other STIs or resistance to BV (Sheih et al 2001). Evidence for enhancement of humoral responses to rotavirus and *Salmonella typhi* has been shown through IgA levels in probiotic treated children and adults (Kaila et al., 1992). Animal and human data suggest that probiotic use is associated with induction of innate and cell-mediated immune responses (Cross 2002), including increased macrophage phagocytic activity (Miettinen et al 2000), complement and reticuloendothelial activation (Gill et al 2000), stimulation of interferon-gamma, interleukin (IL)-12, and IL-18 (Hessle et al., 1999) and increased natural killer cell activity (Matsuzaki and Chin, 2000). However, the major cell wall component of lactobacilli, muramyl dipeptide, can be pyrogenic, and there is concern that lactobacillus enhancement of the T-helper-1 proinflammatory pathway could have negative health consequences (Perdigon and Holgado, 2000). Also, there is concern that the dosage and duration of therapy must be considered so as to optimally enhance and not suppress immunity (Perdigon et al., 1991). Fortunately, probiotic strains have not been found to cause a systemic antibody response (Sheen et al 1995).

Modification of intestinal mucosal immunity by orally administered probiotics may also affect vaginal mucosal immunity to specific pathogens (de Vrese and Schrezenmeir, 2002). In fact, genetic engineering of probiotic bacteria to express pathogen antigens and serve as oral vaccines is being explored (Reveneau et al 2002). In other mucosal vaccine trials, introduction of antigens from HPV and HIV has been accomplished in *S. gordonii* (an oral commensal) and *L. casei*. Local and systemic immune responses were detected in BALB/c mice and Cynomolgus monkeys after vaginal colonization with these strains (Medaglini, 1998). However, there is not yet a good understanding of the relationship between mucosal immunity and BV. In a study of adolescents, BV was found to be inversely associated with lactobacilli counts but was independent of lactobacilli-specific immune responses in isolated peripheral blood leucocytes, and independent of local immune responses measured by antibodies and cytokines measured in cervicovaginal lavages (Alvarez-Olmos et al 2004). In

a study of pregnant women, carriage of a variant of the toll-like receptor-4 gene compared with carriage of the dominant genotype was associated with higher vaginal pH and a 10-fold increase in vaginal *G. vaginalis* levels. Colonization with *G. vaginalis* or anaerobic Gram-negative rods in the dominant allele carriers was associated with elevated vaginal IL-1 and IL-1ra but not in the variant homozygotes (Genc 2004). Probiotic modulation of mucosal immunity may help prevent BV and other STIs including HIV, but it is difficult to predict which strains might do this without knowing the immune correlates of protection and how specific strains will affect these factors. More studies are needed in these areas of scientific enquiry.

## **9. Some clinical evidence of probiotics in helping to reduce the impact of HIV/AIDS**

The increased searchlight on HIV/AIDS care in Africa has been rekindled following financial donations from spirited organizations and individuals on increasing access to antiretroviral (ARV) medication. Nevertheless this is cardinal, efforts are also needed to provide safe and affordable interventions for those without access to ARVs or with CD4 counts too high to initiate ARV therapy, yet whose quality of life is diminished by micronutrient deficiencies, gut infections such as diarrhea, and other complicated conditions associated with HIV infection. The use of micronutrients, most notably vitamin B-complex in combination with C and E, appears to be an effective intervention that have been associated with reduced mortality and in most cases it results in increasing the CD4 counts of the infected person.(Kanter et al., 1991; Kaiser et al., 2006;Jiamton et al., 2003) The WHO/FAO has recommended that an "increased micronutrient intake can be best achieved through an adequate diet,"(WHO, 2003) favoring food-based interventions.

It should be noted that the gastrointestinal tract is one of the most severely affected organ by HIV (Kotler et al., 1984;Sharpstone et al., 1999). Inflammation results in damage to the epithelial barrier, leading to an increased leakage of microbial products into the bloodstream. Recently, it was theorized that this may be an ongoing source of systematic immune activation that fuels HIV (Brenchley, 2006) although this association was less clear in an African population (Redd et al., 2009). Capsule proteins of HIV may further facilitate viral replication by eliciting a profound Th-2 activation that inhibits an effective immune response against the virus (Kanter et al., 1991).

Probiotic bacteria can potentially restore an effective gut barrier (Luyer et al., 2005;Yan et al., 2007) thereby reducing systemic immune activation. Furthermore, probiotics have been shown to upregulate T-regulatory lymphocytes (Baroja et al., 2007;Foligne et al., 2008) potentially skewing the immune system away from a Th-2-dominant state (Mohamadzadeh et al., 2005). Probiotic usage has been shown to be safe among people living with HIV (Wolf et al., 1998;Salminen et al., 2004) and recent randomized trials in Brazil (Trois et al., 2008) and Nigeria (Anukam et al., 2006) suggest that probiotic use can increase the CD4 count. In the Nigerian study, conventional yogurt fermented with *Lactobacillus delbruekii* var *bulgaricus* and *Streptococcus thermophilus* was supplemented with probiotic *Lactobacillus rhamnosus* GR-1 and *L. reuteri* RC-14. Twenty-four HIV/AIDS adult female patients (18 to 44years) with clinical signs of moderate diarrhea, CD4 counts over 200, and not receiving antiretrovirals or dietary supplements, consumed either 100 mL supplemented or unsupplemented yogurt per day for 15 days. Hematologic profiles, CD4 cell counts, and quality of life was evaluated at baseline, 15 and 30 days postprobiotic-yogurt feeding. There was no significant alteration in

the hematologic parameters of both groups before and after the probiotic-yogurt feeding, with the probiotic yogurt group at baseline, 15 and 30 days had a mean WBC count of  $5.8 \pm 0.76 \times 10^9/L$ ,  $6.0 \pm 1.02 \times 10^9/L$ , and  $5.4 \pm 0.14 \times 10^9/L$ , respectively. However, the mean CD4 cell count remained the same or increased at 15 and 30 days in 11/12 probiotic-treated subjects compared to 3/12 in the control. Diarrhea, flatulence, and nausea resolved in 12/12 probiotic-treated subjects within 2 days, compared to 2/12 receiving yogurt for 15 days. This is the first study to show the benefits of probiotic yogurt on quality of life of women in Nigeria with HIV/AIDS, and suggests that perhaps a simple fermented food can provide some relief in the management of the AIDS epidemic in Africa.

The most commonly used vehicle for supplying probiotics; yogurt, is a significant source of vitamin A, B-complex, zinc, and high-biologic-quality protein (Sattler et al., 2008) and is therefore, an excellent food-based intervention to improve micronutrient intake among people living with HIV/AIDS. On the basis of these notions, a community kitchen in Mwanza, Tanzania, was established in 2004 to produce yogurt supplemented with *Lactobacillus rhamnosus* GR-1 (Fiti) to be distributed as an adjunct to the diet of people living with HIV. Irvine et al., (2010) carried out an observational retrospective study over a period of 3 years, with longitudinal comparison of the CD4 count within participants ( $n=68$ ) before and during probiotic yogurt consumption, and compared with a control group of participants not consuming the yogurt ( $n=82$ ). Among the yogurt consumers before use and the nonconsumers, an average increase in CD4 count was seen of 0.13 cells/mL/day (95% CI; 0.07-0.20,  $P<0.001$ ). After commencing consumption, yogurt consumers experienced an additional increase of 0.28 cells/mL/day (95% CI; 0.10-0.46,  $P=0.003$ ). When adjusting for length of time using antiretroviral medication, the additional increase explained by yogurt consumption remained 0.17cells/mL/day (95% CI; 0.01-0.34,  $P=0.04$ ). Treatment with antiretroviral medication was associated with an increase of 0.27 cells/mL/day (95% CI; 0.17-0.38,  $P<0.001$ ). The study concluded that introduction of probiotic yogurt, made by local women in a low-income community in Tanzania, was significantly associated with an increase in CD4 count among consumers living with HIV. Another similar study assessed among women with HIV, whether long-term oral *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 supplementation can prevent bacterial vaginosis (BV) and enhance the cure rate of metronidazole among those with BV. It involved a randomized, double-blind, placebo-controlled trial conducted among 65 HIV-infected women with an aberrant microbiota (Nugent score 4-10) were selected to receive daily probiotics or placebo for 6 months. Those with BV (Nugent score 7-10) additionally received metronidazole for 10 days (400 mg twice daily). Although there was no enhanced cure rate of BV among women with HIV treated with adjuvant probiotics to metronidazole treatment. However, among women with an intermediate vaginal flora, probiotics tended to increase the probability of a normal vaginal flora (odds ratio 2.4;  $P=0.1$ ) and significantly increased the probability of a beneficial vaginal pH (odds ratio 3.8;  $P=0.02$ ) at follow-up (Hummelen et al., 2010)

## 10. Beware of some probiotic claims

While we suggest the potential use of probiotics may be important in ameliorating the impact of urogenital infections in Africa, however there must be caution in terms of controlling the importation of probiotic products. National agencies in Africa in charge of natural products should be prepared to know the probiotic products there are really called probiotics. There are numerous probiotic claims over the internet which may mislead people in buying useless products.

A number of so-called probiotic products claim to be useful for UTI management. Sadly, their marketing hype is not supported by properly performed human studies. US based Natren, makers of probiotic face cream, claim that oral and vaginal GyNaTren helps 'balance the intestinal and vaginal ecology' and should be used to treat vaginitis. No peer-reviewed studies validate this claim. Other products available in Europe, namely Lactovaginal, Gynoflor, Fermalac, Florgynal, Ecovag, Culturelle VC, SymbioFem Plus and Yeast-guard all suffer from lack of appropriate clinical substantiation, and cannot be recommended to prevent UTI. Clearly, companies marketing such products have an obligation to provide evidence of clinical efficacy. This is predicated on the fact that some products may contain different genera, different species, or even different strains of the same species, and not all products should be expected to work the same. Therefore, claims of efficacy should be target specific and should be made only for products that have been found efficacious in carefully designed studies. The marketplace has many examples of different strains of the same species: *Lactobacillus acidophilus* NCFM and La-1; *L. rhamnosus* GR-1 and *L. rhamnosus* GG; *Lactobacillus casei* Shirota and DN-114 001; *Lactobacillus reuteri* RC-14 and ATCC 55730; and *Bifidobacterium lactis* HN019 and BB-12; *Lactobacillus plantarum* WCFS1, *Lactobacillus plantarum* KCA-1. Each of these strains has a unique dossier to document individual health benefits. It is noteworthy, however, that among dozens of European commercial products, the same biotype (based on pulsed-field gel electrophoresis of chromosomal DNA) was predominant among *Bifidobacterium*-containing products (Masco et al., 2005), suggesting that *Bifidobacterium* strains used commercially may not be so diverse. The fact that consumers buy such products suggests that the current management of urogenital infections is not sufficiently well handled by the sole use of antimicrobials. In addition, patients, particularly those suffering from recurrent infections, are well aware of the side effects of antibiotic therapy and the ever-increasing problem of bacterial resistance.

## 11. Can the use of probiotics make an impact in Africa?

The presence of bacterial vaginosis-causing organisms that are perhaps more prevalent in Africa provokes the loss of normal vaginal bacterial flora, and causes vaginal inflammation and increased pH levels. The resulting altered vaginal environment increases the risk of transmission of HIV. In addition diarrhoeal diseases, HIV/AIDS complications, and other infectious diseases are major contributors to morbidity and mortality in sub-Saharan Africa. Morbidity from these illnesses causes economic hardship and mortality results in the loss of the next generation and destruction of the present adult leadership. Several studies have pointed out that the use of probiotics can significantly improve the wellbeing of individuals infected with HIV/AIDS (Anukam, 2007). For example, studies conducted in Africa have estimated the average annual increase in CD4 count of 90 cells/mL with ARV treatment (Lawn et al., 2006) and an average decline of 20 to 50 cells/mL/year without ARV treatment (Holmes et al., 2006; Urassa et al., 2004). In the Tanzanian study, (Irvine et al., 2010), a similar rate of increase was observed of 99 cells/mL with ARV treatment (0.27 cells/mL/d), whereas no significant decrease was observed without ARV treatment. The results of this study indicate that probiotic yogurt consumption is associated with an overall increase in CD4 count of 62 cells/mL/year (0.17 cells/mL/d). This could be due to an accelerated immune reconstitution after initiation of ARV treatment, thus shortening the time of severe immune deficiency, or may be due to an increase in CD4 count among those not yet eligible for ARV treatment, which may potentially delay the need for ARV medication. However, this study is yet to be replicated in other African sites with similar burden of HIV infections.

Indication	Probiotic Genus, Species and Strain	Source and Product format
Vaginal application	<i>Lactobacillus rhamnosus</i> GR-1 and <i>Lactobacillus reuteri</i> RC-14	Fem-Dophilus (capsules) <a href="http://www.urexbiotech.com">www.urexbiotech.com</a> ; <a href="http://www.jarrow.com">www.jarrow.com</a>
Antibiotic associated diarrhea; <i>Clostridium difficile</i>	<i>Saccharomyces cerevisiae</i> ( <i>S. boulardii</i> )	Florastor (powder) <a href="http://www.florastor.com">www.florastor.com</a> Lalflor (capsule) <a href="http://www.institut-rosell.com">www.institut-rosell.com</a>
	<i>L rhamnosus</i> GG	Culturelle (capsule) <a href="http://www.culturelle.com">www.culturelle.com</a> Danimals (drinkable yogurt) <a href="http://www.danimals.com">www.danimals.com</a>
	<i>L casei</i> DN114001	DanActive (fermented milk) <a href="http://www.danactive.com">www.danactive.com</a>
	<i>L acidophilus</i> CL1285 plus <i>L casei</i>	BioK <sup>+</sup> CL1285 (fermented milk, capsule) <a href="http://www.biokplus.com">www.biokplus.com</a>
Gut transit time	<i>B animalis</i> DN173 010 ( <i>Bifidus regularis</i> )	Activia (yogurt) <a href="http://www.activia.com">www.activia.com</a>
Infant diarrhea	<i>L rhamnosus</i> GG (LGG)	Culturelle (capsule) <a href="http://www.culturelle.com">www.culturelle.com</a> Danimals (drinkable yogurt) <a href="http://www.danimals.com">www.danimals.com</a>
	<i>L casei</i> DN114001 (Immunitas)	DanActive (fermented milk) <a href="http://www.danactive.com">www.danactive.com</a>
Inflammatory bowel conditions (primary evidence in pouchitis)	8-strain combination of 3 <i>Bifidobacterium</i> strains, 4 <i>Lactobacillus</i> strains and <i>S. thermophilus</i>	VSL#3 (powder) <a href="http://www.vsl3.com">www.vsl3.com</a>
Keeping healthy	<i>L reuteri</i> ATCC 55730	BioGaia Chewable Gut Health Tablets, BioGaia Gut Health Probiotic Straws, <a href="http://www.everidis.com">www.everidis.com</a>
Lactose intolerance	Most strains <i>L bulgaricus</i> and/or <i>S thermophilus</i>	All yogurts with live, active cultures
Immune support	<i>B lactis</i> HN019 (HOWARU or DR10)	Strain sold as an ingredient for dairy and supplement products – contact Danisco <a href="http://www.danisco.com">www.danisco.com</a>
	<i>B lactis</i> Bb-12	Good Start Natural Cultures (infant formula) <a href="http://www.verybestbaby.com/GoodStart/Overview.aspx">www.verybestbaby.com/GoodStart/Overview.aspx</a> Yo-Plus (yogurt) <a href="http://www.yo-plus.com">www.yo-plus.com</a>
	<i>L casei</i> DN114001	DanActive (fermented milk) <a href="http://www.danactive.com">www.danactive.com</a>

Table 2. Some probiotic products with published clinical studies

## 12. Conclusions

Several studies have shown that probiotics could enhance the health and well-being of individuals in sub-Saharan Africa, but sadly the use of probiotics has not become popular for several reasons outlined by Anukam and Reid (2005). First, pharmaceutical companies that manufacture probiotics would be forced to lower prices, which would adversely affect their revenues. Secondly, storage and distribution problems make the allocation of probiotics difficult. Dairy versions of probiotics require refrigeration, and other forms incorporated in tablets, capsules, and powders must be retained in proper vials with appropriate desiccants. Accordingly, storage and distribution issues present major challenges to the effective implementation of probiotic treatment since domestic technology is frequently insufficient for proper maintenance. Finally, cultural acceptance presents a major challenge for probiotic use. For example, if local customs call for a diet free of dairy products, it could be difficult to convince these people to consume a fermented milk drink.

The lack of any probiotic fermented food products in Africa at present, with the exception of a grass roots community kitchen in Tanzania where probiotic *Lactobacillus rhamnosus* GR-1 is used ([www.westernheadseast.ca](http://www.westernheadseast.ca)), makes it difficult to perform studies and provide benefits to the population. Until this happens, hopefully with clinically proven products and not simply ones where the term probiotic is used or bacteria are added as an ingredient without testing, indigenous fermented foods may be explored further as a source of health benefits.

While many fermented foods are eaten in Africa soon after being produced, the lack of refrigerated distribution networks makes it difficult to reach a large population. In this context, McMaster et al., (2005), developed a microencapsulation delivery system for *Bifidobacterium lactis* DSM 10140, which if successfully applied to foods might overcome some of the shelf-life problems faced by lack of refrigeration. The study used two existing traditional fermented foods, "amasi" and "mahewu." The gellan/xanthan microcapsules containing viable *B. lactis* were tested under simulated physiological conditions and added to pasteurized beverages. The results showed protection of the organism in low pH and against the biocidal activity of pancreatic and bile acids. For "mahewu," microencapsulation of *B. lactis* with storage aerobically at 4°C and 22°C enhanced survival over a 21-day period compared to free cells. This is still not reflective of extreme temperatures found in Africa, so further studies are needed to confirm if this method will lead to making 'mahewu' available to people.

In confirming the validity of evidence on probiotics, the United Nations Food and Agriculture Organization and the World Health Organization (WHO/FAO, 2001) sponsored an Expert Consultation in 2001. The resulting Report stressed that "Efforts should be made to make probiotic products more widely available, especially for relief work and populations at high risk of morbidity and mortality". Eleven years later, this clarion call to the healthcare community and to the food industries in providing probiotics to the people of sub-Saharan Africa has yet to be answered.

With the increasing number of people living and dying of AIDS, only a few people have easy access to life-prolonging antiretroviral drug therapy. The HIV/AIDS pandemic is propelled by social, cultural and economic gender inequalities that limit children and women's ability to protect themselves from infection. The main strategies by UNAIDS for HIV prevention are promotion of condoms, reducing the number of sexual partners, and treatment of reproductive tract infections. These strategies are laudable but not feasible for many women. Occasionally, it may seem appropriate to provide perspective and to



verbalize concerns and disquietude anytime the UN publishes the life expectancy of the people from developing countries. No one has taken the pain to ask the question why the Japanese, coincidentally with a long history of probiotic consumption, have the highest life expectancy in the world today and low HIV prevalence (<0.1%, contributed through contaminated blood products) (Oelrichs, 2004), while the people from sub-Saharan Africa, coincidentally with no classically defined probiotic consumption, have the lowest life expectancy in the world, and the highest HIV prevalence. Besides, there are no available probiotics to boost the immune system (Gill et al., 2002), treat diarrhea and prevent urogenital infections.

More studies and interest are needed to expand our understanding of this approach to healthcare in sub-Saharan Africa, to knowing their limitations and understanding their mechanisms of action, and examining economic, social, political and behavioral changes for more expansive introduction of probiotic concepts. Hopefully, concerted research efforts will stimulate other scientists, students, and physicians to explore this area. The development of recombinant strains expressing potent anti-HIV microbicides may provide a more specific preventive approach in future years.

Making probiotic products available to both the uninfected and infected persons, gives them opportunity to choose among other health promoting products. Probiotics may be a viable paradigm towards reducing the risk associated with acquisition of HIV mostly in women by restoring the vaginal microbiota and help relieve the suffering of AIDS patients, most of who suffer from chronic diarrhea.

### 13. Acknowledgement

Dr. Kingsley C Anukam research on probiotic genomics is funded by the Academy of Sciences for the Developing World (TWAS).

### 14. References

- Altman, L (2002) 'By 2010, AIDS May Leave 20 Million African Orphans'. *New York Times*; 11:A-10.
- Alvarez-Olmos MI, Barousse MM, Rajan L, et al., (2004). Vaginal lactobacilli in adolescents: Presence and relationship to local and systemic immunity, and to bacterial vaginosis. *Sex Transm Dis*, 31:393-400.
- Amsel R, Totten PA, Spiegel CA, et al., (1983). Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations. *Am J Med*, 74:14-22
- Antonio MA, Rabe LK, Hillier SL. (2005). Colonization of the rectum by *Lactobacillus* species and decreased risk of bacterial vaginosis. *J Infect Dis*. 192(3):394-8.
- Antonio MA, Hawes SE, Hillier SL. (1999). The identification of vaginal *Lactobacillus* species and the demographic and microbiologic characteristics of women colonized by these species. *J Infect Dis* 180:1950-1956.
- Anukam KC, Macklaim JM, Gloor GB, Reid G, Seizen R (2011). Genome sequencing of *Lactobacillus plantarum* KCA-1, a potential probiotic lactic acid bacterium isolated from the vagina of a healthy Nigerian woman. *Joint International Conference of the African and South African Societies of Human Genetics*, Cape Town, South Africa, 6-9 March 2011. Poster 013.

- Anukam KC, Osazuwa EO, Ahonkhai I, Reid G. (2006). Lactobacillus vaginal microbiota of women attending a reproductive health care service in Benin City, Nigeria. *Sex Trans Dis*. 33(1): 59-62
- Anukam KC, Osazuwa EO, Ahonkhai I, Ngwu M, Osemene G, Bruce AW and Reid G (2006a). Augmentation of antimicrobial metronidazole therapy of bacterial vaginosis with oral probiotic *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14: randomized, double-blind, placebo controlled trial. *Microbes Infect*, 8 (6):1450-1454
- Anukam KC, Osazuwa E, Osemene GI, Ehigiagbe F, Bruce AW, Reid G (2006b). Clinical study comparing probiotic *Lactobacillus* GR-1 and RC-14 with metronidazole vaginal gel to treat symptomatic bacterial vaginosis. *Microbes Infect*, 8 (12-13):2772-2776.
- Anukam KC, Osazuwa EO, Osadolor HB, et al. (2008). Yogurt containing probiotic *Lactobacillus rhamnosus* GR-1 and *L. reuteri* RC-14 helps resolve moderate diarrhea and increases CD4 count in HIV/AIDS patients. *J Clin Gastroenterol*. 42:239-243.
- Anukam KC (2007). The potential role of probiotics in reducing poverty-associated infections in developing countries. *J Infect Developing Countries*, 1(2):81-83.
- Anukam K, Reid G (2005). Providing probiotics to sub-Saharan Africa: ethical principles to consider. *J Complementary and Integrative Med*, 2: Article 10.
- Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, et al. (2005) Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 trial. *PLoS Med* 2(11): e298.
- Bailey RC, Moses S, Parker CB, Agot K, Maclean I, et al. (2007). Male circumcision for HIV prevention in young men in Kisumu, Kenya: A randomised controlled trial. *Lancet*, 369(9562): 643-656.
- Baroja ML, Kirjavainen PV, Hekmat S, et al., (2007). Anti-inflammatory effects of probiotic yogurt in inflammatory bowel disease patients. *Clinical Experimental Immunol*, 149:470-479
- Bolton M, Straten AV, Cohen CR (2008). Probiotics: potential to prevent HIV and sexually transmitted infections in women. *Sex Trans Dis*, 35(3):214-225.
- Botos I, Wlodawer A (2005). Proteins that bind high-mannose sugars of the HIV envelope. *Prog Biophys Mol Biol*, 88:233-282.
- Brenchley JM, Price DA, Schacker TW, et al., (2006). Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nat Med*.12:1365-1371.
- Bruce AW, Reid G (1988). Intravaginal instillation of lactobacilli for prevention of recurrent urinary tract infections. *Can J Microbiol*. 34:339-343.
- Caillouette JC, Sharp CF Jr, Zimmerman GJ, et al. , (1997). Vaginal pH as a marker for bacterial pathogens and menopausal status. *Am J Obstet Gynecol*, 176:1270-1275; discussion 5-7.
- Chancey CJ, Khanna KV, Seegers JF, et al., (2006). Lactobacilli-expressed single-chain variable fragment (scFv) specific for intercellular adhesion molecule 1 (ICAM-1) blocks cell-associated HIV-1 transmission across a cervical epithelial monolayer. *J Immunol*. 176:5627-5636.
- Chang TL, Chang CH, Simpson DA, et al., (2003). Inhibition of HIV infectivity by a natural human isolate of *Lactobacillus jensenii* engineered to express functional two-domain CD4. *Proc Natl Acad Sci U S A*, 100:11672-11677.

- Cherpes TL, Meyn LA, Krohn MA, et al., (2003). Association between acquisition of herpes simplex virus type 2 in women and bacterial vaginosis. *Clin Infect Dis*, 37:319-325
- Cross ML (2002). Microbes versus microbes: Immune signals generated by probiotic lactobacilli and their role in protection against microbial pathogens. *FEMS Immunol Med Microbiol*, 34:245-253
- DeBaets AJ, Bulterys M, Abrams EJ, Kankassa C, Pazvakavambwa IE (2007). Care and treatment of HIV-infected children in Africa: issues and challenges at the district hospital level. *Pediatr Infect Dis J*, 26(2):163-173
- de Jong MA, Geijtenbeek TB (2009). Human immunodeficiency virus-1 acquisition in genital mucosa: Langerhans cells as key-players. *J Intern Med*, 265(1): 18-28.
- Delia A, Morgante G, Rago G, Musacchio MC, Petraglia F, De Leo V (2006). Effectiveness of oral administration of *Lactobacillus paracasei* subsp. *paracasei* F19 in association with vaginal suppositories of *Lactobacillus acidophilus* in the treatment of vaginosis and in the prevention of recurrent vaginitis. *Minerva Ginecol*. 58(3):227-31.
- de Vrese M, Schrezenmeir J (2002). Probiotics and non-intestinal infectious conditions. *Br J Nutr*, 88(suppl 1):S59-S66.
- Ellis AK, Verma S. (2000). Quality of life in women with urinary tract infections: is benign disease a misnomer? *J Am Board Fam Pract*, 13:392-397.
- Eschenbach DA, Davick PR, William BL, et al. (1989). Prevalence of hydrogen peroxide-producing *Lactobacillus* species in normal women and women with bacterial vaginosis. *J Clin Microbiol*, 27:251-256.
- Ewaschuk JB, Backer JL, Churchill TA, et al., (2007). Surface expression of Toll-like receptor 9 is upregulated on intestinal epithelial cells in response to pathogenic bacterial DNA. *Infect Immun*, 75:2572-2579.
- Falagas ME, Betsi GI, Tokas T, Athanasiou S (2006). Probiotics for prevention of recurrent urinary tract infections in women: a review of the evidence from microbiological and clinical studies. *Drugs*. 66(9):1253-61
- Ferris DG, Dekle C, Litaker MS (1996). Women's use of over-the-counter antifungal medications for gynecologic symptoms. *J Fam Pract*, 42:595-600.
- Foligne B, Zoumpopoulou G, Dewulf J, et al., (2007). A key role of dendritic cells in probiotic functionality. *PLoS ONE*, 2:e313.
- Fredricks DN, Fiedler TL, Thomas KK, et al.,(2007). Targeted polymerase- chain-reaction for the detection of vaginal bacteria associated with bacterial vaginosis. *J Clin Microbiol*, 45:3270-3276.
- Galvin SR, Cohen MS (2004). The role of sexually transmitted diseases in HIV transmission. *Nat Rev Microbiol*, 2(1): 33-42.
- Genc MR, Vardhana S, Delaney ML, et al., (2004). Relationship between a toll-like receptor-4 gene polymorphism, bacterial vaginosis-related flora and vaginal cytokine responses in pregnant women. *Eur J Obstet Gynecol Reprod Biol*, 116:152-156
- Gill HS, Rutherford KJ, Prasad J, et al., (2002). Enhancement of natural and acquired immunity by *Lactobacillus rhamnosus* (HN001), *Lactobacillus acidophilus* (HN017) and *Bifidobacterium lactis* (HN019) *Br J Nutr*, 83:167-176.
- Ginkel PD, Soper DE, Bump RC, et al., (1993). The vaginal flora in post-menopausal women: The effect of estrogen replacement. *Infect Dis Obstet Gynecol*, 1:94.
- Gray RH, Kigozi G, Serwadda D, Makumbi F, Nalugoda F, et al. (2009). The effects of male circumcision on female partners' genital tract symptoms and vaginal infections in a randomized trial in rakai, uganda. *Am J Obstet Gynecol*, 200(1): 42.e1-42.e7.

- Hay PE, Lamont RF, Taylor-Robinson D, Morgan DJ, Ison C, Pearson J (1994). Abnormal bacterial colonisation of the genital tract and subsequent preterm delivery and late miscarriage. *Bmj*, 308(6924):295-298
- Hay P. (2000). Recurrent bacterial vaginosis. *Curr Infect Dis Rep*, 2: 506-512.
- Hessle C, Hanson LA, Wold AE (1999). Lactobacilli from human gastrointestinal mucosa are strong stimulators of IL-12 production. *Clin Exp Immunol*, 116:276-282.
- Hillebrand L, Harmanli OH, Whiteman V, Khandelwal M (2002). Urinary tract infections in pregnant women with bacterial vaginosis. *Am J Obstet Gynecol*, 186(5):916-917
- Hoesl CE, Altwein JE (2005). The probiotic approach: an alternative treatment option in urology. *Eur Urol.*, 47(3):288-96
- Hummelen R, Changalucha J, Butamanya NL, Cook A, Habbema JDF, Reid G (2010). *Lactobacillus rhamnosus* GR-1 and *L.reuteri* RC-14 to prevent or cure bacterial vaginosis among women with HIV, *Int J Gynecol Obstet*, doi:10.1016/j.ijgo.2010.07.008
- Irvine SL, Hummelen R, Hekmat S, Looman CWN, Habbema JDF, Reid G (2010). Probiotic yogurt consumption is associated with an increase of CD4 count among people living with HIV/AIDS. *J Clin Gastroenterol*, 44:e201-e205.
- Holmes C, Wood R, Badri M, et al., (2006). CD4 decline and incidence of opportunistic infections in Cape Town, South Africa: implications for prophylaxis and treatment. *J Acquired Immune Deficiency Syndromes*, 42:464-469.
- Jiamton S, Pepin J, Suttent R (2003). A randomized trial of the impact of multiple micronutrient supplementation on mortality among HIV-infected individuals living in Bangkok. *AIDS* (London, England), 17:2461-2469.
- Kaila M, Isolauri E, Soppi E, et al., (1992). Enhancement of the circulating antibody secreting cell response in human diarrhea by a human *Lactobacillus* strain. *Pediatr Res*, 32:141-144.
- Kanter AS, Spencer DC, Steinberg MH, et al., (1999). Supplemental vitamin B and progression to AIDS and death in black South African patients infected with HIV. *J Acquir Immune Defic Syndr*, 21:252-253.
- Kaiser JD, Adriana MC, Ondercin JP, et al. Micronutrient supplementation increases CD4 count in HIV-infected individuals on highly active antiretroviral therapy: a prospective, double-blinded, placebo-controlled trial. *J Acquired Immune Deficiency Syndromes* (1999). 2006;42:523-528.
- Keane FE, Ison CA, Taylor-Robinson D (1997). A longitudinal study of the vaginal flora over a menstrual cycle. *Int J STD AIDS* 8:489-494.
- Kim SO, Sheikh HI, Ha S, Martins A, Reid G (2006). G-CSF-mediated inhibition of JNK is a key mechanism for *Lactobacillus rhamnosus*-induced suppression of TNF production in macrophages. *Cell Microbiol*, 8(12), 1958-1971.
- Kirjavainen P K, Laine RM, Carter D, Hammond JA, Reid G. 2008. Expression of antimicrobial defense factors in vaginal mucosa following exposure to *Lactobacillus rhamnosus* GR-1. *Int. J. Probiotics*. 3: 99-106.
- Klebanoff SJ, Coombs RW (1991a). Viricidal effect of *Lactobacillus acidophilus* on human immunodeficiency virus type 1: Possible role in heterosexual transmission. *J Exp Med*, 174:289-292.
- Klebanoff SJ, Hillier SL, Eschenbach DA, et al (1991b). Control of the microbial flora of the vagina by H2O2-generating lactobacilli. *J Infect Dis*, 164:94-100

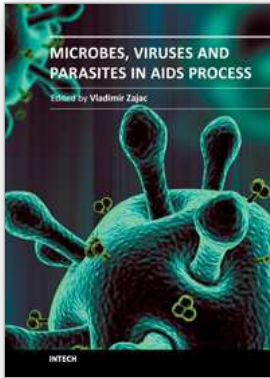
- Klebanoff MA, Schwebke JR, Zhang J, Nansel TR, Yu KF, Andrews WW (2004). Vulvovaginal symptoms in women with bacterial vaginosis. *Obstet Gynecol*, 104(2):267-72
- Kline MW (2006). Perspectives on the pediatric HIV/AIDS pandemic: catalyzing access of children to care and treatment. *Pediatrics*, 117(4):1388-1393.
- Kotler DP, Gaetz HP, Lange M, et al., (1984). Enteropathy associated with the acquired immunodeficiency syndrome. *Ann Intern Med*, 101:421-428.
- Laughton J, Devillard E, Heinrichs D, Reid G, McCormick J. (2006). Inhibition of expression of a staphylococcal superantigen-like protein by a secreted signaling factor from *Lactobacillus reuteri*. *Microbiology*, 152: 1155-1167
- Lawn SD, Myer L, Bekker LG, et al., (2006). CD4 cell count recovery among HIV-infected patients with very advanced immunodeficiency commencing antiretroviral treatment in sub-Saharan Africa. *BMC Infectious Diseases*, 6:59.
- Liu X, Lagenaur LA, Simpson DA, et al., (2006). Engineered vaginal *Lactobacillus* strain for mucosal delivery of the human immunodeficiency virus inhibitor cyanovirin-N. *Antimicrob Agents Chemother*, 50:3250-3259.
- Liu JJ, Reid G, Jiang Y, et al., (2006). Activity of HIV entry and fusion inhibitors expressed by the human vaginal colonizing probiotic *Lactobacillus reuteri* RC-14. *Cell Microbiol*, 31:31.
- Livengood CH, Soper DE, Sheehan KL, et al. (1999). Comparison of once-daily and twice-daily dosing of 0.75% metronidazole gel in the treatment of bacterial vaginosis. *Sex Transm Dis*, 26:137-142.
- Luyer MD, Buurman WA, Hadfoune M, et al. (2005). Strain-specific effects of probiotics on gut barrier integrity following hemorrhagic shock. *Infection Immunity*, 73:3686-3692.
- Martin HL, Richardson BA, Nyange PM, et al., (1999). Vaginal lactobacilli, microbial flora, and risk of human immunodeficiency virus type 1 and sexually transmitted disease acquisition. *J Infect Dis*. 180:1863-1868.
- Masco L, Huys G, De Brandt E, et al., (2005). Culture-dependent and culture-independent qualitative analysis of probiotic products claimed to contain bifidobacteria. *Int J Food Microbiol*, 102:221-30.
- Matsuzaki T, Chin J (2000). Modulating immune responses with probiotic bacteria. *Immunol Cell Biol*, 78:67-73.
- McCombe SG, Short RV (2006) Potential HIV-1 target cells in the human penis. *AIDS*, 20(11): 1491-1495.
- McMaster LD, Kokott SA, Reid SJ, Abratt VR (2005). Use of traditional African fermented beverages as delivery vehicles for *Bifidobacterium lactis* DSM 10140. *Int J Food Microbiol*, 102:231-237.
- McNeil D (2010). At Front Lines: AIDS War is Falling Apart. *New York Time*, May 8.
- Medaglini D, Oggioni MR, Pozzi G (1998). Vaginal immunization with recombinant gram-positive bacteria. *Am J Reprod Immunol* 39:199 -208
- Miettinen M, Lehtonen A, Julkunen I, et al., (2000). Lactobacilli and Streptococci activate NF-kappa B and STAT signaling pathways in human macrophages. *J Immunol*, 164:3733-3740
- Mohamadzadeh M, Olson S, Kalina WV, et al (2005). Lactobacilli activate human dendritic cells that skew T cells toward T helper 1 polarization. *Proc Natl Aca Sci USA*.102:2880-2885
- MSF (2009). *HIV/AIDS treatment in developing countries: The battle for long-term survival has just begun*. Geneva: Médecins Sans Frontières

- Naidu AS, Bidlack WR, Clemens RA (1999). Probiotic spectra of lactic acid bacteria (LAB). *Crit Rev Food Sci Nutr*, 39:13–126
- Nugent RP, Krohn MA, Hillier SL (1991). Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. *J Clin Microbiol*, 29:297–301.
- Oakeshott P, Hay P, Hay S, Steinke F, Rink E, Kerry S (2002). Association between bacterial vaginosis or chlamydial infection and miscarriage before 16 weeks' gestation: prospective community based cohort study. *Bmj*, 325(7376):1334
- Oelrichs R, (2004). The subtypes of human immunodeficiency virus in Australia and Asia. *Sexual Health* 1:1-11.
- Patterson BK, Landay A, Siegel JN, Flener Z, Pessis D, et al. (2002) Susceptibility to human immunodeficiency virus-1 infection of human foreskin and cervical tissue grown in explant culture. *Am J Pathol*, 161(3): 867–873.
- Perdigon G, Alvarez S, Pesce de Ruiz Holgado A (1991). Immunoadjuvant activity of oral *Lactobacillus casei*: Influence of dose on the secretory immune response and protective capacity in intestinal infections. *J Dairy Res*, 58:485–496
- Perdigon G, Holgado APdR (2000). Mechanisms involved in the immunostimulation by lactic acid bacteria. In: Perdigon G, Fuller R, eds. *Probiotics*. Amsterdam, The Netherlands: Kluwer Academic, 213–233.
- Price LB, Liu CM, Johnson KE, Aziz M, Lau MK, et al. (2010) The Effects of Circumcision on the Penis Microbiome. *PLoS ONE* 5(1): e8422. doi:10.1371/journal.pone.0008422.
- Pusch O, Boden D, Hannify S, et al., (2005). Bioengineering lactic acid bacteria to secrete the HIV-1 virucide cyanovirin. *J Acquir Immune Defic Syndr*, 40:512–520.
- Pusch O, Kalyanaraman R, Tucker LD, et al., (2006). An anti-HIV microbicide engineered in commensal bacteria: Secretion of HIV-1 fusion inhibitors by lactobacilli. *AIDS*, 20:1917–1922.
- Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, et al., (2004). Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. *Cell*, 118:229–241.
- Rao S, Hu S, McHugh L, et al., (2005). Toward a live microbial microbicide for HIV: Commensal bacteria secreting an HIV fusion inhibitor peptide. *Proc Natl Acad Sci U S A*, 102:11993–11998.
- Ravel J, Gajer P, Abdo Z, Schneider GM, Koenig SK, McCulle SL, Karlebach S, Gorle R, Russell J, Tacket CO, Brotman RM,
- Davis CC, Ault K, Peralta L, Forney LJ (2011). Vaginal microbiome of reproductive-age women. *Proc Natl Acad Sci USA*, 108: 4680–4687.
- Redd AD, Dabita D, Bream JH, et al., (2009). Microbial translocation, the innate cytokine response, and HIV-1 disease progression in Africa. *Proc Natl Acad Sci USA*, 106:6718–6723
- Reid G, Bruce AW, Cook RL, Llano M.(1990). Effect on the urogenital flora of antibiotic therapy for urinary tract infection. *Scand J Infect Dis*, 22:43–7
- Reid G, Bruce AW, Taylor M (1995). Instillation of *Lactobacillus* and stimulation of indigenous organisms to prevent recurrence of urinary tract infections. *Microecol. Ther.* 23:32–45.
- Reid G. (1999). The scientific basis for probiotic strains of *Lactobacillus*. *Appl Environ Microbiol*, 65:3763–3766.
- Reid G, Beuerman D, Heinemann C, Bruce AW (2001). Probiotic *Lactobacillus* dose required to restore and maintain a normal vaginal flora. *FEMS Immunol. Med. Microbiol*, 32: 37–41

- Reid G, Bruce AW, Fraser N, et al., (2001). Oral probiotics can resolve urogenital infections. *FEMS Microbiol Immunol.* 30:49–52.
- Reid G, Bruce AW (2006). Probiotics to prevent urinary tract infections: the rationale and evidence. *World J Urol.* 24(1):28-32.
- Reid G, Charbonneau D, Erb J, et al. (2003). Oral use of *Lactobacillus rhamnosus* GR-1 and *L. fermentum* RC-14 significantly alters vaginal flora: randomized, placebo-controlled trial. *FEMS Immunol Med Microbiol*, 35:131–134.
- Report (2009). National HIV/AIDS Sentinel Seroprevalence Survey. Federal Ministry of Health (FMOH), Abuja, Nigeria. 20
- Reveneau N, Geoffroy MC, Loch C, et al., (2002). Comparison of the immune responses induced by local immunizations with recombinant *Lactobacillus plantarum* producing tetanus toxin fragment C in different cellular locations. *Vaccine*, 20(13–14): 1769–1777.
- Salminen MK, Tynkkynen S, Rautelin H, et al., (2004). The efficacy and safety of probiotic *Lactobacillus rhamnosus* GG on prolonged, noninfectious diarrhea in HIV patients on anti- retroviral therapy: a randomized, placebo-controlled, cross- over study. *HIV Clinical Trials*, 5:183–191.
- Sattler FR, Rajicic N, Mulligan K, et al., (2008). Evaluation of high-protein supplementation in weight-stable HIV-positive subjects with a history of weight loss: a randomized, double- blind, multicenter trial. *American J Clinical Nutr.* 88: 1313–1321.
- Sengupta, (2002). “U.N. Session Begins to Tally the Perils of Being Young”. *New York Times*, 9:A- 14.
- Sewankambo N, Gray RH, Wawer MJ, et al., (1997). HIV- 1 infection associated with abnormal vaginal flora morphology and bacterial vaginosis. *Lancet*, 350:546-550
- Sharpstone D, Neild P, Crane R, et al., (1999). Small intestinal transit, absorption, and permeability in patients with AIDS with and without diarrhoea. *Gut*, 45:70–76.
- Sheen P, Oberhelman RA, Gilman RH, et al., (1995). Short report: A placebo-controlled study of *Lactobacillus* GG colonization in one-to-three-year-old Peruvian children. *Am J Trop Med Hyg.* 52:389–392.
- Sheih YH, Chiang BL, Wang LH, et al., (2001). Systemic immunity-enhancing effects in healthy subjects following dietary consumption of the lactic acid bacterium *Lactobacillus rhamnosus* HN001. *J Am Coll Nutr* 20(2 suppl):149–156
- Silva M, Jacobus NV, Deneke C, et al., (1987). Antimicrobial substance from a human *Lactobacillus* strain. *Antimicrob Agents Chemother* , 31:1231–1233.
- Smart S, Singal A, Mindel A (2004). Social and sexual risk factors for bacterial vaginosis. *Sex Transm Infect*, 80(1):58-62.
- Sorek R, Kunin V, Hugenholtz P (2008). CRISPR—a widespread system that provides acquired resistance against phage in bacteria and archaea. *Nat. Rev. Microbiol.* 6:181–186
- St Amant DC, Valentin-Bon IE, Jerse AE (2002). Inhibition of *Neisseria gonorrhoeae* by *Lactobacillus* species that are commonly isolated from the female genital tract. *Infect Immun*, 70:7169–7171
- Taha TE, Hoover DR, Dallabetta GA, et al. (1999). Bacterial vaginosis and disturbances of vaginal flora: association with increased acquisition of HIV. *AIDS.* 12:1699-706.
- UNAIDS (2009). *Report on the Global AIDS Epidemic.* Geneva.
- UNAIDS (2002). Press release. “UNAIDS Releases New Data Highlighting the Devastating Impact of AIDS in Africa.”

- [http://www.unaids/whatsnew/press/eng/pressarc02/G8\\_250602.html](http://www.unaids/whatsnew/press/eng/pressarc02/G8_250602.html) (accessed 4 July 2010)
- Urassa W, Bakari M, Sandstrom E, et al. , (2004). Rate of decline of absolute number and percentage of CD4T lymphocytes among HIV-1-infected adults in Dar es Salaam, Tanzania. *AIDS*, 18:433–438.
- Vale PF, Little TJ. (2010). CRISPR-mediated phage resistance and the ghost of coevolution past. *Proc. R. Soc. Lond. B Biol. Sci.* 277:2097–2103
- Van Niekerk A(2001). 'Moral and Social Complexities of AIDS in Africa'. *Journal of Medicine and Philosophy*, 27;2: 144
- Verhelst R, Verstraelen H, Claeys G, et al., (2005). Comparison between Gram stain and culture for the characterization of vaginal microflora: Definition of a distinct grade that resembles grade I microflora and revised categorization of grade I microflora. *BMC Microbiol*, 5:61.
- Walker WA, Goulet O, Morelli L, Antoine JM(2006). Progress in the science of probiotics: from cellular microbiology and applied immunology to clinical nutrition. *Eur J Nutr.* 45 Suppl 9:1-18
- Wiesenfeld HC, Hillier SL, Krohn MA, Lander DV, Swet RL (2003). Bacterial vaginosis is a strong predictor of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infection. *Clin Infect Dis*, 36:663-668.
- Wilson JD, Ralph SG, Rutherford AJ (2002). Rates of bacterial vaginosis in women undergoing in vitro fertilisation for different types of infertility. *Bjog*, 109(6):714-717
- WHO/FAO (2001). Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria, a joint FAO/WHO expert consultation. [WHO website] October 1–4. Available at: [www.who.int/foodsafety/publications/fs\\_management/en/probiotics.pdf](http://www.who.int/foodsafety/publications/fs_management/en/probiotics.pdf) Accessed March 30, 2011.
- WHO (2003). Technical Consultation on Nutrient Requirements for People Living with HIV/AIDS. Available at: [http://www.who.int/nutrition/publications/Content\\_nutrient\\_requirements.pdf](http://www.who.int/nutrition/publications/Content_nutrient_requirements.pdf). Accessed March 30, 2011.
- Wolf BW, Wheeler KB, Ataya DG, et al., (1998). Safety and tolerance of *Lactobacillus reuteri* supplementation to a population infected with the human immunodeficiency virus. *Food Chem Toxicol.* 36:1085–1094.
- Yan F, Cao H, Cover TL, et al., (2007). Soluble proteins produced by probiotic bacteria regulate intestinal epithelial cell survival and growth. *Gastroenterology*, 132:562–575.
- Zyrek AA, Cichon C, Helms S, et al., (2007). Molecular mechanisms underlying the probiotic effects of *Escherichia coli* Nissie 1917 involve ZO-2 and PKCzeta redistribution resulting in tight junction and epithelial barrier repair. *Cell Microbiol*, 9:804–816





## **Microbes, Viruses and Parasites in AIDS Process**

Edited by Prof. Vladimír Zajac

ISBN 978-953-307-601-0

Hard cover, 390 pages

**Publisher** InTech

**Published online** 19, October, 2011

**Published in print edition** October, 2011

The main goal in compiling this book was to highlight the situation in Africa in terms of AIDS and opportunistic diseases. Several chapters reveal great poverty, an apocalyptic situation in many parts of Africa. Global migration of people resulted in their exposure to pathogens from all over the world. This fact has to be acknowledged and accepted as African reality. New, unconventional hypotheses, not determined by established dogmas, have been incorporated into the book, although they have not yet been sufficiently validated experimentally. It still applies that any dogma in any area of science, and medicine in particular, has and always will hinder progress. According to some biologists, in the future, AIDS is very likely to occur in a number of variations, as a direct result of the ongoing processes in the global human society. Thus, we urgently need a comprehensive solution for AIDS, in order to be ready to fight other, much more dangerous intruders.

### **How to reference**

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

Kingsley C. Anukam, Enya B. Bassey and Emmanuel O. Osazuwa (2011). Reducing Urogenital Infections Including HIV in Sub-Saharan Africa - Can Probiotics Be a Viable Paradigm?, *Microbes, Viruses and Parasites in AIDS Process*, Prof. Vladimír Zajac (Ed.), ISBN: 978-953-307-601-0, InTech, Available from: <http://www.intechopen.com/books/microbes-viruses-and-parasites-in-aids-process/reducing-urogenital-infections-including-hiv-in-sub-saharan-africa-can-probiotics-be-a-viable-paradi>

# **INTECH**

open science | open minds

### **InTech Europe**

University Campus STeP Ri  
Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166  
[www.intechopen.com](http://www.intechopen.com)

### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.