

# A cultured response to HIV



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In recent years, research has continued to demonstrate that HIV wreaks terrible havoc in the gut. A few scientists believe that probiotic yogurt might help to counter some of the virus's devastating effects on the intestine. **Melinda Wenner** reports on a pilot project that is helping a Tanzanian community make its own probiotic yogurt for HIV-infected locals and empowering women in the process.

Every morning, 54-year-old Elizabeth Gabeal walks from her home in the small village of Mabatini, Tanzania to a small community kitchen. The tiny space is known as Jiko la Maziwa Imara, Swahili for 'the kitchen of milk strength'. Gabeal and the nine other 'yogurt mamas' who work alongside her spend the day transforming local farmers' milk—delivered each morning by bicycle—into a probiotic yogurt. In addition to selling 200 servings a day to community residents for a profit, they also give free cups away to 125 people with HIV/AIDS in the hopes that the yogurt might make them healthier.

Gabeal, who raised eight children alone after her husband abandoned her, says that

the yogurt kitchen has not only helped her children grow up to be strong but also made her a stronger woman. "It allows us to empower our family, afford for ourselves," she says.

The kitchen is the fruit of a pilot project called Western Heads East, based out of the University of Western Ontario in Canada. Since 2004, the program has sent 22 undergraduate and graduate interns to Mabatini to teach the ten yogurt mamas, all of whom are mothers, how to make yogurt with scientifically developed probiotics—and build a sustainable business.

The hope is that in addition to empowering the mamas and providing extra nutrition to impoverished locals, the yogurt will also offer

unique health benefits to the HIV-positive residents of Mabatini. Small studies suggest that in HIV-positive individuals, probiotics can improve immune cell counts and alleviate diarrhea and lower the risk of HIV transmission by curbing risk factors such as bacterial vaginosis infections.

## Homing in on yogurt

Western Heads East, an unusual project, is an idea hatched by a group of college housing administrators. In 2002, the housing staff from Ontario universities asked Stephen Lewis, a Canadian and, at the time, United Nations Special Envoy for HIV/AIDS in Africa, to speak at one of the meetings they had organized. To

emphasize the need for humanitarian aid in Africa, Lewis compared the AIDS pandemic there to the 9/11 attacks in the US, which claimed nearly 3,000 lives.

“Lewis said, ‘Every day in Africa, 3,000 people die—and the world stands by and watches,’ recalls Bob Gough, assistant director of residence programs at the University of Western Ontario. That comparison struck a chord with some of the audience members, including Gough; a few started crying. ‘All of us felt the same way,’ Gough says. ‘We were thinking, ‘Ok, we have to do something—what are we going to do?’”

The group of college administrators assembled a steering committee to brainstorm. Soon after, Gough stumbled across a local newspaper article about Gregor Reid, the assistant director of the Lawson Health Research Institute, the research arm of the University of Western Ontario’s teaching hospital.

Reid, who has studied the health benefits of probiotics since 1982, had recently helped develop a probiotic yogurt with the help of nutritional scientist Sharareh Hekmat. Probiotics are live microorganisms—typically bacteria—that provide health benefits when ingested or administered in adequate amounts. These products primarily influence the intestine, which is home to an estimated 100 trillion bacteria important for immunity and digestion<sup>1</sup>.

Reid had some evidence hinting that his probiotic, *Lactobacillus rhamnosus* GR-1, could help clear bacterial vaginosis infections<sup>2</sup> (which seem to increase the risk of acquiring

HIV) and boost the production of immune cells in people with irritable bowel syndrome by nearly 50%<sup>3</sup>.

At that point, there had been little research on the effects of probiotics on people with HIV—but circumstantial evidence suggested that they might be beneficial. So Gough invited Reid to address the steering committee, and Reid easily convinced them to make the yogurt a focus of their project. “We knew that, of course, the probiotic yogurt is not a cure for AIDS,” says Gough, “but it’s something that would help.”

### Gut thinking

In 1984, the year after HIV was identified as the infectious agent that causes AIDS, immunologist Donald Kotler of Saint Luke’s–Roosevelt Hospital Center in New York noted<sup>4</sup> that HIV-infected individuals show severe gut abnormalities. Several years later, researchers identified the gastrointestinal tract as a site of considerable early HIV replication and CD4+ T cell destruction<sup>5</sup>. (The gut contains an abundance of T cells—the immune cells preferentially attacked by HIV.)

“It’s almost like the gut is a magnet for the virus early on. [It] becomes compromised in weeks,” says Bill Critchfield, a postdoctoral fellow at the University of California–Davis. With this in mind, Critchfield is helping recruit people with HIV for a small clinical trial to assess the effects of probiotics with added fiber.

The destruction of immune cells in the gut severely damages the intestine’s mucosa and might have a role in disease progression, according to an article authored by Daniel Douek and his colleagues at the US National Institute of Allergy and Infectious Diseases in Bethesda, Maryland<sup>6</sup>. The immunologists found high levels of lipopolysaccharide—a molecule found in the outer membrane of Gram-negative bacteria—circulating in the bloodstreams of individuals infected with HIV. The discovery suggested that bacteria were possibly leaking across the broken gut barrier into the blood.

Douek and his teammates proposed that these circulating microbial products caused the chronic immune system activation that is a hallmark of HIV (blood levels of proinflammatory cytokines are much higher in HIV-positive individuals than in uninfected people). There is also some evidence to suggest that this activation accelerates the progression of HIV to AIDS, by encouraging the production of activated T cells for HIV to infect and destroy<sup>7</sup> and by damaging lymphoid tissues<sup>8</sup>.

The obvious question, then, is whether blocking the first step of the cascade—the



Microbes in the mix: *Lactobacillus* bacteria

leaky gut—could prevent HIV from propelling forward and ultimately keep infected individuals healthier. Animal studies have suggested that probiotics can repair leaky gut. For example, one study showed that 87% of rats with short bowel syndrome—a disorder typically caused by surgical removal of the small intestine—suffer from a leaky gut, but only 50% do if they are given probiotics<sup>9</sup>.

Probiotics might also protect HIV-infected individuals from other infections. In healthy people, the gut is home to thousands of species of beneficial microbes, but the microbial balance can become skewed during HIV infection. Two studies published last year suggest that HIV-positive people also suffer a loss of a subset of gut T cells called T helper type 17 cells, which are thought to be crucial defenders against disease-causing bacteria and fungi<sup>10,11</sup>. Without these immune cells, the gut can become overwrought with pathogenic microbes—and, thanks to the leaky gut, these microbes might end up in the bloodstream as well.

Probiotics might help restore gut health by out-competing pathogens for nutrients or secreting antimicrobial substances, as some studies suggest<sup>12,13</sup>. This, according to Douek, makes probiotics “well worth trying” to improve the health of HIV-infected individuals.

### Mixed results

With \$17,000 of funding from the university’s development office and international research fund and some small personal donations, Western Heads East sent its first two interns to Mabatini in January 2005 to do just that.



Milking it: Yogurt itself has nutritional value



Douglas Keady/University of Western Ontario

**Sign of hope:** A sign outside the Mabatini kitchen advertizes “Fiti”, the probiotic yogurt

First, the interns had to teach the yogurt mamas how to make the yogurt and establish the current protocol. Every morning, farmers deliver milk to the kitchen, and the women in the group measure its density to make sure the farmers did not dilute it with water. They then pasteurize the milk with heat and, once it’s cooled, inoculate it with standard yogurt bacteria cultures and the probiotic bacteria—*L. rhamnosus* GR-1—which the Tanzanian National Institute for Medical Research, several miles away, stores and provides to them every week. They incubate the yogurt for six to eight hours, move it to a refrigerator for two days, and then distribute the product.

With the help of the program supported by Western Heads East, Reid and his colleagues are now studying the HIV-positive subjects in the Mabatini community to see if the yogurt will improve CD4+ T cell counts. They believe that it will; in a small pilot study his group organized in Canada that is currently being submitted for publication, *L. rhamnosus* GR-2 yogurt supplemented with micronutrients increased CD4+ cell count by 19 to 41 cells per microliter of blood in a group of HIV-infected individuals.

Meanwhile, researchers in Brazil have already published data from a trial involving 77 HIV-positive children showing that a two-month course of probiotic formula increased CD4+ T cell counts by 17.5%, compared with a decrease of 7% in the control group<sup>14</sup>.

A study in Nigeria led by Reid’s group failed

to find a dramatic effect on CD4+ T cell counts from probiotics<sup>15</sup>. But the preliminary data they have obtained in Mabatini seem more promising.

They have found, for example, that a 10-week course of probiotic capsules containing *L. rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 increased mean CD4+ cell counts by 15% among HIV-positive women (the control group of HIV-positive women experienced a slight decrease).

Still, because HIV preferentially targets and replicates in CD4+ T cells, Douek points out that any therapy that increases T cell counts should be accompanied by antiretroviral therapies that reduce viral load. “One has to look at all of these different aspects of therapy simultaneously,” he says.

“I think it’s worthwhile to try and understand how microbiota in the intestine interact with the immune system, for sure,” says Dan Littman, a professor of molecular immunology at New York University and an expert on HIV pathogenesis. “But how that relates to HIV infection at this point, I think it’s too early to say.”

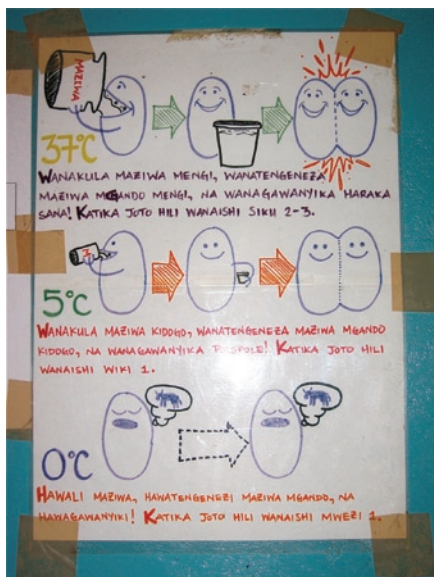
Although the jury remains out on the immune system effects of probiotics, proponents say that probiotics might be able to improve the lives of HIV-infected people in other ways, by improving nutrition and alleviating chronic diarrhea (diarrhea afflicts up to 90% of people living with HIV/AIDS in developing countries)<sup>16</sup>. A preliminary study published in 2004<sup>17</sup> found that probiotic supplements with added fiber resolved diarrhea symptoms in 10 of 28 HIV-positive individuals, whereas seven controls experienced no changes. The idea is that probiotics might alleviate diarrhea because they tip the balance of microflora in the gut away from pathogenic microbes such as *Escherichia coli*.

Reid contends that probiotics may also be able to help, at least in women, by staving off a common vaginal infection known as bacterial vaginosis, which seems to increase the risk of HIV infection. His team conducted a study involving 64 women that found that those receiving an antibiotic-probiotic combination



Gregor Reid

**Taste testing:** Children in the Mabatini community sample the yogurt



Douglas Keddy/University of Western Ontario

### Yogurt cues: Directions in the Mababini Kitchen

had a bacterial vaginosis cure rate of 90%, compared with 50% among the control group who were given the antibiotic with a placebo<sup>18</sup>. His previous work has suggested that probiotic oral supplements help maintain healthy vaginal microflora<sup>19</sup>. Reid and his colleagues are now designing a study to test the effects of the probiotic yogurt on bacterial vaginosis rates in Mababini.

### Starting small

These Mababini studies haven't exactly been easy to conduct for a number of reasons. First, there's sample size—only 125 HIV-infected individuals regularly receive the yogurt. These low numbers “make it difficult to do the studies

and to publish with a high impact,” Reid says. There have been many communication problems, too, especially considering that the mamas have no background in science. “You're taking mothers who've spent a life looking after families, and now you're telling them how to make a product and how to do it reliably, safely, reproducibly,” Reid says.

For example, at one point, the interns discovered that the mamas weren't adding the probiotic to the yogurt as instructed. Another time, they heard that some locals had stopped taking their antiretroviral therapy, believing the yogurt to be an HIV cure. There have also been plenty of technological hurdles; electrical power in the kitchen is sporadic, and transportation options are limited. “The simple things you deal with every day here [in Canada] are so much more difficult there,” explains Sabrina Mullan, who interned for the project from June 2008 to April 2009. “I didn't really expect all the challenges.”

Despite these hiccups, the yogurt mamas are excited to keep the kitchen going. “They are so proud of the work that they are doing,” says Gough, who most recently visited Mababini this past fall. Last year, the mamas licensed their kitchen as a nongovernmental organization, and they have received funding to buy their own cows for milking. In addition, the university recently purchased an acre of land so that the community can build a bigger kitchen and expand the business. The mamas are spreading their wisdom, too—they have taught women in two neighboring communities and in Kenya how to make the yogurt, and they plan to teach women in Rwanda and Uganda eventually.

Gough believes that the project not

only provides direct health benefits to the community but also has sociological and psychological payoffs. The mamas “have more autonomy and are just more secure in themselves,” he says. One has recently started counseling local women about spousal abuse; another has started advising residents who have been diagnosed with HIV. Perhaps, says Nancy Padian, director of the Women's Global Health Imperative at RTI International in San Francisco, the empowerment these women experience could also help slow the spread of HIV in their communities. “If you give women an opportunity to be economically independent and also have hope for the future, they'll be better in the position to help themselves,” she says. “They're more in control over who they have sex with and under what circumstances.”

It might seem counterintuitive that bacteria could boost the health of a third-world community and improve HIV symptoms. But “bacteria are completely integral to life on the planet,” Reid says, so “it shouldn't be surprising that we're studying their benefits in humans.” He admits that there are still many more questions about probiotics than there are answers—but he hopes that in the coming decade, Western Heads East and its unique research model will reverse that trend.

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Douglas Keddy/University of Western Ontario

Mama mia! The 'Yogurt mamas' in Mababini making the probiotic food