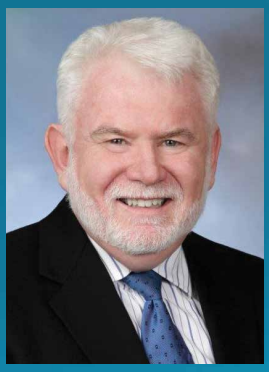
THE PROMISE OF PREVENTION FOR WOMEN

2014 ANNUAL REPORT

INTERNATIONAL PARTNERSHIP *for* MICROBICIDES

Dr. Zeda F. Rosenberg
Chief Executive Officer



Dr. James McIntyre
Chair of the Board

Dear friends and colleagues,

In our offices in South Africa and the United States hang placards bearing an important daily reminder of IPM's mission: to put safe and effective microbicides in the hands of women. Every day, we face the sobering fact that women and girls remain at high risk of HIV infection. This year, we are excited to be preparing for the possibility that the monthly dapivirine ring could soon offer women a new way to protect their health.

The continuing high rates of new HIV infections in women underscore the importance of acting quickly should the dapivirine ring prove effective. With efficacy results from the two parallel Phase III trials of the ring expected by early 2016, IPM has intensified its regulatory and access planning. By preparing now, we can maximize the ring's potential public health impact.

During a year when the global community is setting goals for improving women's health and sustainable development, the HIV prevention research field is at a critical juncture. As the recent FACTS 001 results highlighted, women—especially young women in sub-Saharan Africa—need HIV prevention methods they can and will use. Research to develop new products must continue alongside efforts to better understand the role of oral pre-exposure prophylaxis, or PrEP, as an HIV prevention tool for women.

In addition to the dapivirine ring, IPM is advancing a variety of promising technologies that would expand women's prevention options. This year, we will initiate a first-in-human clinical trial of a vaginal tablet containing a new antiretroviral (ARV) drug, DS003, which will be developed further as a long-acting vaginal ring. A Phase I trial of IPM's 90-day dapivirine-contraceptive ring designed to simultaneously prevent HIV and unintended pregnancy is expected to begin in early 2016. We are also supporting several trials of different vaginal and rectal formulations of various ARVs.

From the time IPM was founded in 2002, we have marshalled scientific know-how, creative partnerships and resources to develop lifesaving tools for women's sexual and reproductive health. With the support and relentless commitment of countless clinical trial volunteers, donors and partners, that reality is coming into sharper focus.

Zeda F. Rosenberg

Dr. Zeda F. Rosenberg

James McIntyre

Dr. James McIntyre

Every day, nearly 2,500 women worldwide are infected with HIV. In sub-Saharan Africa, young women are at least twice as likely to be infected as young men. Moreover, 225 million women worldwide have an unmet need for family planning. Women critically need a range of new prevention tools that match their individual needs and fit into the context of their lives.

Expanding and sustaining a diverse product pipeline is vital to helping prevent HIV over time and supporting women's sexual and reproductive health. IPM is responding with a robust, cutting-edge pipeline of long-acting female-initiated products.

Dapivirine Ring

Designed to:	**Protect women against HIV**
Formulation:	**Self-inserted flexible silicone matrix vaginal ring designed for one-month protection, with a three-month ring in development**
Active ingredient:	**Dapivirine (ARV)**
Mechanism of action:	**Non-nucleoside reverse transcriptase inhibitor (NNRTI) that blocks HIV's ability to replicate itself in healthy cells**

A Brief History of the Ring

From the beginning, IPM focused on identifying potent ARVs that could be harnessed for safe and easy-to-use microbicide products. In 2004, IPM was approached by Janssen Sciences Ireland UC, a Janssen pharmaceutical company of Johnson & Johnson, and negotiated a royalty-free license to develop the ARV drug dapivirine as a topical microbicide for women's HIV prevention in developing countries. This license expanded to an exclusive worldwide rights agreement in 2014.

From 2004 to 2010, IPM evaluated dapivirine in an extensive program of preclinical assessments and clinical studies. In 2010, we prioritized a ring formulation that would provide discreet, long-acting protection to women. Building on early prototypes, IPM developed the current monthly dapivirine ring in collaboration with Queens University Belfast (QUB). From 2009 to 2014, IPM completed a series of safety and pharmacokinetics studies of the ring, as well as acceptability research showing that vaginal rings were highly acceptable to women and their male partners, and that women are willing to use a ring if it prevents HIV.

First Efficacy Trials of a Long-Acting Microbicide

After advancing the dapivirine ring from an idea to Phase III trials in just seven years, IPM launched the Dapivirine Ring Licensure Program in 2012. Because regulatory authorities usually require data from at least two large-scale efficacy trials along with supporting studies to approve a product, IPM designed a program to supply the necessary data comprehensively and efficiently.

Given the ring's promise, the US National Institutes of Health-funded Microbicide Trials Network (MTN) joined the licensure program as a clinical trial partner to keep the time line to regulatory approval as short as possible. This program includes two parallel Phase III trials: The Ring Study, led by IPM, and the ASPIRE study, led by MTN. Both studies reached full enrollment in 2014, with more than 4,500 women enrolled across Malawi, South Africa, Uganda and Zimbabwe. The ASPIRE study completed participant follow-up in June 2015, while The Ring Study, which was designed to collect long-term safety data, continues until late 2016. Final results from ASPIRE as well as efficacy and preliminary safety results from The Ring Study are expected by early 2016.

Focusing on retention and adherence: IPM continues to work actively with research center staff, participants and communities to keep them engaged in the trials and encourage product adherence through outreach events and educational activities. In addition, The Ring Study uses objective adherence measures such as assessing the amount of dapivirine remaining in used rings as well as drug levels in plasma and vaginal fluid samples, all in addition to data from interviews and questionnaires.

Supporting studies: A package of smaller studies required for regulatory approval also moved ahead in 2014. IPM completed studies on dapivirine's interaction with a drug commonly used to treat vaginal yeast infections, the ring's compatibility with female and male condoms, and extended use of the ring. In addition, IPM initiated a study of sociobehavioral factors of adherence. In collaboration with MTN, we initiated studies on safety in adolescent females and safety in women over 45. IPM planned for a study on the effects of menses and tampon use on the ring, now under way, as well as a second drug interaction study.

Preparing for an Effective Microbicide

To get an effective ring into women's hands as quickly as possible, IPM planned for potential licensure and access from the ring's initial development and throughout the research process. As the dapivirine ring's developer and regulatory sponsor, IPM engages partners to lay the groundwork for the ring's regulatory submission, manufacturing, distribution, financing and access.

After efficacy: open-label studies: Should the ring prove effective, women who participated in the Phase III studies would be given access to the active ring. All participants who are still enrolled in The Ring Study would receive active rings for the remainder of their participation. In addition, IPM and MTN would each initiate a Phase IIIb follow-on study to provide all previous Ring Study and ASPIRE participants with the active ring for at least one year while the product is undergoing review by regulatory authorities for broad distribution. The Phase IIIb studies would also collect additional safety and adherence data.

On the Regulatory Pathway: The Dapivirine Dossier

IPM continues to consult with the European Medicines Agency, US Food and Drug Administration, South African Medicines Control Council and additional African regulatory authorities to ensure we meet regulatory data requirements. These data are being organized into a global dossier on the dapivirine ring containing information on everything from its ingredients to findings from nearly 250 studies of dapivirine over 13 years. Compiling this master electronic file will allow us to quickly adapt the dossier for future country-specific regulatory submissions.

Roadmap to Access

Introducing and scaling up a new product requires a deep network of resources and collaborations. In 2014, IPM drafted a comprehensive plan to facilitate affordable and sustainable access to a future dapivirine ring. As part of this plan, we selected QPharma, which completed ring manufacturing for the licensure program in 2014, as our launch manufacturing partner. IPM also planned a suite of studies and activities now under way to drive the ring's distribution, financing and use, pending efficacy results. These include a cost-effectiveness study, strategies to ensure adequate funding and political support, and supply and distribution partner selection. IPM is also working on advocacy, awareness-raising and training activities for groups key to successful product introduction — from women to civil society organizations to health workers and many others.

Recognizing that product access strategies will need to be tailored to specific regions, IPM is meeting with stakeholders in countries where the ring would be introduced. These partnerships expand our understanding of market dynamics, public policy, and the cultural, financial and other factors that affect women's willingness and ability to access a future ring.

A staff member processes samples for The Ring Study at the Desmond Tutu HIV Foundation in Masiphumulele, South Africa.

Staff at Maternal, Adolescent and Child Health (MatCH) in Kwazulu-Natal, South Africa, celebrate The Ring Study reaching full enrollment in 2014.

A staff member organizes blood samples for The Ring Study at the Uganda Virus Research Institute in Masaka, Uganda.

Dapivirine-Contraceptive Ring

The dual threats to women's health from HIV/AIDS and complications due to unintended pregnancy are not a burden women should have to bear. Under a USAID grant through PEPFAR, IPM is adapting its vaginal ring to provide women with a self-initiated three-month multipurpose prevention technology (MPT) designed to prevent both HIV and unintended pregnancy.

Expanding Women's Sexual and Reproductive Health Options

IPM's MPT ring combines dapivirine, an ARV, and levonorgestrel, a contraceptive hormone. In 2014, after evaluating multiple ring designs and materials, IPM expanded the MPT ring's target length of action from two months to three months, and collaborated with QUB to develop a flexible silicone matrix prototype.

IPM is partnering with MTN to conduct a Phase I pharmacokinetics and safety trial of the three-month MPT ring in the United States to begin in early 2016. As the regulatory sponsor for this first-in-human trial, IPM initiated plans to ensure sufficient drug supplies for the trial, and selected QPharma to manufacture Good Manufacturing Practice-quality rings.

MPT collaborations: IPM is also providing placebo vaginal rings for the Bill & Melinda Gates Foundation-funded TRIO study assessing the acceptability of ring, oral tablet and injectable MPT formulations among South African and Kenyan women. Led by RTI International, the study is expected to begin in 2015.

DS003 Tablet and Ring

To outsmart the ever-evolving HIV virus over the long term, IPM is exploring new drugs that use alternative mechanisms of action. A gp120 binder, DS003 is a promising ARV candidate because it directly targets HIV and acts early in the virus's lifecycle to block HIV's ability to enter healthy cells.

IPM is studying several DS003 formulations for women, including a single-use vaginal tablet (in collaboration with the University of South Australia) and a three-month vaginal ring (in collaboration with QUB).

In 2014, IPM initiated preclinical toxicology and pharmacokinetics studies on DS003. Based on encouraging results of these and previous preclinical tests, IPM plans to lead a Phase I safety and tolerability trial of the DS003 tablet in late 2015. The findings from that first-in-human trial will be used to inform development of a long-acting vaginal ring that would combine DS003 with another ARV.

IPM negotiated with Bristol-Myers Squibb for a royalty-free worldwide license to DS003 in 2005.

"It's more important than ever that alternative methods of HIV prevention for women are developed."

– Naledi Pandor, South African Minister of Science and Technology

Controlled-release delivery system being explored for dapivirine-maraviroc ring. Photo courtesy of Oak Crest Institute of Science.

Dapivirine-Maraviroc Ring

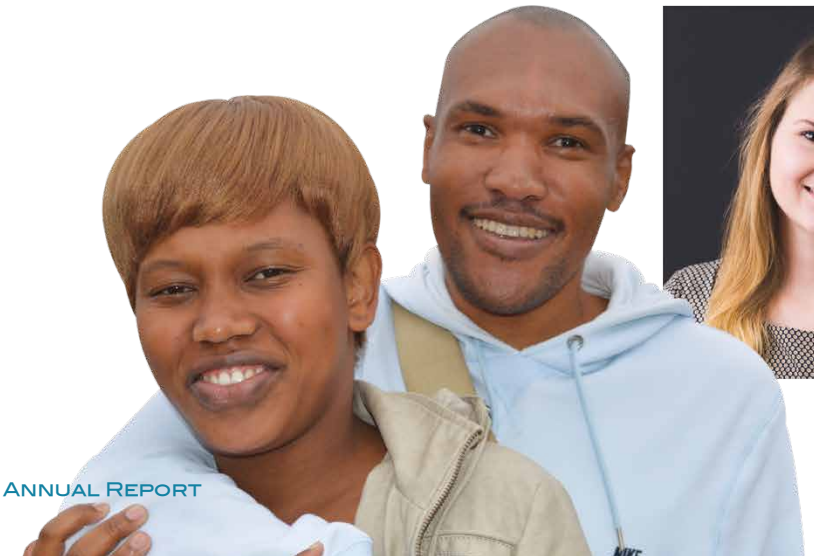
Combination ARV products may offer greater protection against HIV than a single drug alone. IPM's one-month combination vaginal ring leverages two potent ARVs with different mechanisms of action: dapivirine, an NNRTI, and maraviroc, a CCR5 receptor antagonist that blocks HIV's ability to enter healthy cells. The first combination microbicide to enter clinical trials for HIV prevention, the ring was found in 2014 to be safe, well-tolerated and acceptable in a Phase I trial conducted in partnership with MTN. To optimize the formulation to target higher release levels of maraviroc, IPM is partnering with the Oak Crest Institute of Science to explore its controlled-release ring delivery system that uses embedded ARV-loaded pods to release the active drugs.

IPM began developing maraviroc, an ARV currently used for oral HIV treatment, as a microbicide in 2008 through a royalty-free licensing agreement held by ViiV Healthcare.

Dapivirine-Darunavir Ring and Gel

IPM is investigating different formulations of darunavir, a protease inhibitor that blocks HIV's ability to produce viable virus, and is currently used orally to treat HIV. Working with the European Commission-funded CHAARM project, preclinical studies of the pharmacokinetics and efficacy of a one-month dapivirine-darunavir vaginal ring were completed in 2014.

Following preclinical toxicology studies of a daily dapivirine-darunavir vaginal gel led by CHAARM in 2014, IPM supplied clinical materials for a Phase I trial initiated in 2015 at the University of York in England. The safety and pharmacokinetics study is evaluating a single dose and daily use of the combination gel, with a darunavir-only gel arm for comparison.



Other Pipeline Products

IPM is collaborating with research partners on other promising microbicide products, including:

- ***Dapivirine vaginal film.*** In 2014, Johns Hopkins University completed a Phase I trial of the single-use dapivirine vaginal film. Developed in collaboration with the NIH-funded Magee-Womens Research Institute FAME program, the film was found to produce encouraging dapivirine levels in cervical tissue. With IPM's support, the FAME program is also investigating combination films, including a dapivirine-DS003 vaginal film.
- ***Maraviroc-based rectal gel.*** In 2014, IPM oversaw the production of clinical supplies and received approval to begin a Phase I trial of maraviroc-based gel. The CHARM-03 trial was launched in 2015 by the NIH-funded CHARM program at the University of Pittsburgh, comparing maraviroc in gels used rectally and vaginally as well as in oral pills in women and men.
- ***Dapivirine rectal gel.*** IPM is partnering with MTN for a Phase I trial in 2015 to evaluate the safety and pharmacokinetics of dapivirine gel used rectally by women and men. A second Phase I trial is planned for 2016 in conjunction with MTN and product developer CONRAD.

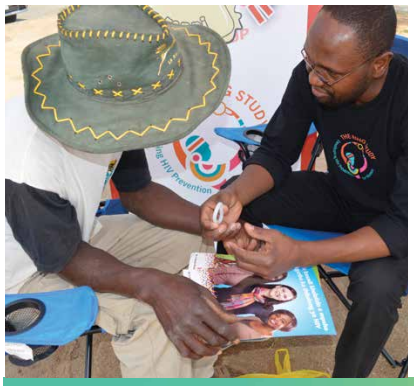
Building Awareness

IPM continues to engage trial communities, civil society and government partners through community events, briefings and information-sharing to support health and research literacy, and to gather feedback that informs our research and access planning. In 2014, outreach activities continued in collaboration with advocacy organizations such as the Southern African AIDS Trust in Malawi and Zimbabwe, the Kenya Medical Women's Association, AIDS-Fondet in Denmark, Sex og Politikk in Norway and Aids Fonds in the Netherlands.

Civil society consultations: IPM, together with MTN and the HIV prevention advocacy organization AVAC, held a series of consultations in 2014 in Malawi, South Africa, Uganda and Zimbabwe with nearly 150 civil society representatives to solicit feedback on the preliminary designs for future open-label Phase IIIb studies of the dapivirine ring. This input informed the study protocols submitted to research ethics committees in late 2014. IPM will build on these consultations while planning for product roll-out.

In August 2014, IPM, MTN and AVAC met with civil society representatives in Malawi as part of a series of consultations in the four countries where the Phase III dapivirine ring trials are taking place.

Engaging stakeholders to plan for access: In 2014, IPM undertook an educational outreach campaign to raise awareness of microbicides generally and the ring specifically in Kenya, Malawi and Zimbabwe. Health workers advised on the information they would need to recommend a future ring and on education programs. Policymakers shared ideas on stakeholders and initiatives needed to build support for the ring.



A staff member of Ndlovu Care Group in Limpopo, South Africa, describes the ring during an educational session to engage men in HIV prevention research.

Tools for Health Workers and Policymakers

IPM incorporated findings from its qualitative study of health workers' microbicide knowledge and perceptions into a suite of new materials to familiarize health workers and policymakers with the ring and how it is used. These materials will be used for future educational campaigns during product roll-out, should the ring prove effective.

Advocating for a healthy future: The well-being of women and girls must be prioritized to encourage sustainable growth. In 2014, IPM and its partners began advocating for the inclusion of HIV/AIDS prevention and sexual and reproductive health priorities in the Sustainable Development Goals, which outline a global vision for the next 15 years and are now being finalized by the United Nations. IPM's pipeline is designed to empower women to protect themselves, slow the HIV epidemic and support healthy, productive societies.

IPM's CEO Dr. Zeda Rosenberg highlighted women's HIV prevention needs as part of FHI360's video interview series for the 20th International AIDS Conference in Melbourne, Australia.

IPM's Chief Medical Officer Dr. Annalene Nel

IPM co-authored or supported 30 oral and poster presentations at the inaugural HIV R4P Conference, focused on biomedical HIV prevention research. Senior IPM staff also co-chaired two oral abstract sessions at the Cape Town conference.

IPM's Senior Director of Product Development Dr. Jeremy Nuttall

IPM's Technical Lead of Analytical Sciences Dr. Stephen Ampofo

Leading with science: IPM's work was presented at many major scientific conferences in 2014. Highlights include results from Phase I studies of the dapivirine film and dapivirine-maraviroc ring at the Conference on Retroviruses and Opportunistic Infections in Boston, and dapivirine ring and MPT ring research at the HIV Research for Prevention (R4P) Conference in Cape Town, South Africa.

IPM published research on the dapivirine ring, gel and film in journals such as *AIDS*, the *Journal of AIDS & Clinical Research, AIDS Research and Human Retroviruses,* and *Molecular Pharmaceutics.* IPM also published articles on sociobehavioral research in the *Journal of the International AIDS Society* and on MPTs in a special supplement to *BJOG: An International Journal of Obstetrics & Gynaecology*.

IPM Donors

Current Donors

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Ministry of Foreign Affairs of Denmark

Ministry of Foreign Affairs of the Netherlands

Norwegian Agency for Development Cooperation, Norwegian Ministry of Foreign Affairs

United Kingdom Department for International Development

United States Agency for International Development through the United States President's Emergency Plan for AIDS Relief

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European Commission

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M•A•C AIDS Fund

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2014 Financial Considerations

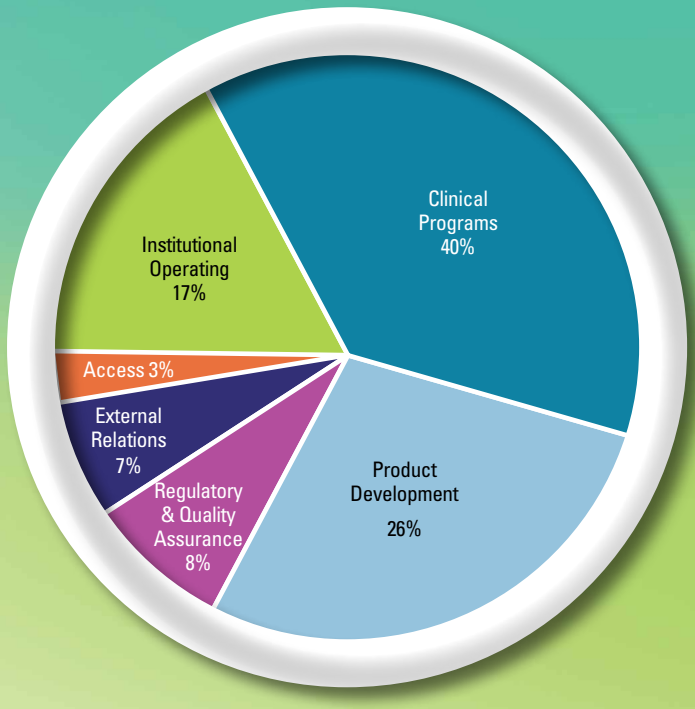
IPM's cash, cash equivalents and short-term investments as of December 31, 2014 totaled USD 23.7 million. During 2014, IPM continued to increase clinical research center expenditures in Africa in support of The Ring Study, one of two parallel Phase III clinical trials of the dapivirine ring. Seven research centers are participating in the ongoing clinical study. Significant expenditures for chemistry, manufacturing and control activities as well as a robust clinical infrastructure support this pivotal trial. In addition, IPM increased its activities in FY 2014 to prepare for access to a potentially effective ring.

In 2014, IPM received approximately USD 22 million from eight donors, including significant awards from USAID, DFID, the Ministry of Foreign Affairs of the Netherlands, Irish Aid and the Bill & Melinda Gates Foundation. We also continued to receive important support from our other donors. IPM is in compliance with all financial reporting requirements from all domestic, international government and private donors, and has received unqualified, or clean, opinions on all audits in both our US and South Africa offices.

With new funding received in 2014, IPM also advanced its product pipeline, an integral component of the organization's strategy beyond the Dapivirine Ring Licensure Program. In consultation with its Scientific Advisory Board, IPM will continue to apply a highly disciplined approach to product prioritization that advances only the most promising self-initiated HIV prevention tools and other sexual and reproductive health technologies for women.

IPM's Board of Directors, management team and staff are committed to efficiently and effectively delivering on our mission to advance new methods to protect women around the world from HIV infection. Because sustained donor funding for IPM's success is essential to achieving our mission, we continue to advocate for increased funds from existing donors and pursue new sources of support to achieve our goals.

EXPENSES BY DEPARTMENT



ASSETS	DEC. 31, 2014
Cash and cash equivalents	$17,211,932
Investments, at market	$6,444,218
Accounts receivable	$3,253,478
Prepaid expenses and other current assets	$1,160,959
Property and equipment, net	$802,435
Total Assets	**$28,873,022**

LIABILITIES AND NET ASSETS	
Liabilities	
Accounts payable and accrued expenses	$2,308,972
Grant advances and deferred revenue	$11,778,472
Total Liabilities	**$14,087,444**
Net Assets — unrestricted	$14,785,578

"We need to fast track female-controlled HIV prevention methods."

–Michel Sidibé, Executive Director, UNAIDS

Learn more about how to promote women's health worldwide and save millions of lives at www.IPMglobal.org

Follow us on Twitter at @IPMicrobicides

INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

IPM Headquarters

8401 Colesville Road
Suite 200
Silver Spring, MD 20910 USA
Tel: +1-301-608-2221
Fax: +1-301-608-2241

IPM South Africa

63 Main Road
Paarl 7646, South Africa
P.O. Box 3460
Tel: +27-21-860-2300
Fax: +27-21-860-3208/1000