# Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Baeten JM, Palanee-Phillips T, Brown ER, et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. N Engl J Med 2016;375:2121-32. DOI: 10.1056/NEJMoa1506110

## Table of Contents, Supplementary Material

### *MTN-020/ASPIRE*

**MTN-020/ASPIRE Study Team:**

**Malawi: Blantyre site (Malawi College of Medicine-John Hopkins University Research Project):** Effie Stephanie Bello, Martha Chihana, Jacqueline Chiphwanya Huwa, Patience Chisale, Flora Chithila, Sufia S. Dadabhai, Leslie Degnan, Barbara Debevec,Tiferanji Fatch, Esther Goliati, Daniel Kondwani Gondwe, Dumisile Huwa Kandonje, Evans Kachale, Victoria Kaliwo, Madalitso Kamaliza, Melvin Kamanga, Mary Kamanga Chadza, Dean Kamangadazi Soko, Thokozani Kaphiri, Newton Kumwenda, Wezi Longwe Mwenda, Blessings Madiwati, Bonus Makanani, Jennie Makunganya, Agness Malemia, Martha Malidadi, Abel Maruwo, Yamikani Rose Mbilizi, Jayne Mpofu, Phyllis Mulenga, Joyce Mulima, Jossen Munthali Lines Mwafulirwa, Thoko Mwakhwawa, Linda Njete, Kondwani Nkanaunena, Mary Nyirenda, Mariana Phingo, Grace Phiri, Linly Seyama, Harry Simkoza, Isaac Singini, Andrea Singini, Edith Sitima, Alex Siyasiya, Taha Taha, Frank Taulo, Edna Taulo, Titus Tung'ande, Fatima Zulu

**Malawi: Lilongwe site (University of North Carolina Project):** Chimwemwe Baluwa, Gabriel Banda, Blessings Banda, Towera Banda, Linda Chikopa, Mary Chindebvu, Joseph Chintedza, Lameck Chinula, Fred Chitema, Gladys Chitsulo, Grace Chiudzu, Nelecy Chome, Ntchindi Gondwe, Irving Hoffman, Emma Kachipapa, Ivy Kaliati, Angella Kalulu, Getrude Kamwana, Jane Kilembe, Madawa Kumwenda, Wiza Kumwenda, Phaleda Kumwenda, Thandie Lungu, Chalimba Lusewa, Yvonne Makala, Clement Mapanje, Francis Martinson, Wongani Mhango, Nkhafwire Mkandawire, Tawonga Mkochi, Emmie Msiska, Lusungu Msumba, Mathews Mukatipa, Joyce Mwese, Margret Ndovie, Thokozani Nkhalamba, Naomi Nyirenda, Dorothy Sichali, Hannah Stambuli, Gerald Tegha, Tapiwa Tembo, Tchangani Tembo

**South Africa: Cape Town site (University of Cape Town):** Millicent Atujuna, Shaun Barnabas, Linda-Gail Bekker, Dyan Belonje, Nomsa Cengimbo, Harrite Achu Chabanga, Thobeka Coba, Danielle Crida, Jacqueline Dallimore, Nwabisa Danster, Siphuxolo Dikili, Riana Dippenaar, Penina Dlulane, Pamella Dukwe, Lindelwa Dyabeni, Llewellyn Fleurs, Nosiphelo Pretty Funda, Jennipher Gelant, Litha Gogo, Sibusiso Gumede, Nondumiso Hlwele, Thandiwe Hobongwana, Lindsay Jeffery, Maria Jose, Babalwa Khaya, Thembisile Khumalo, Nicola Killa, Melanie Maclachlan, Nocwaka Magobiane, Ferial Mahed, Pamela Makhamba, Gakiema Malan, Avril Masters, Nombongo Mayekiso, Thobelani Mcayiya, Bukiwe Mngqebisa, Noxolo Mona, Zanoxolo Mthethi, Norah Nandudu, Bungane Ngayi, Nontshukumo Ngqabe, Sivuyile Max Nkomiyapi, Mluleleki Nompondwana, Vuyokazi Ntlantsana, Mzamo Ntshoko, Nazmie Pearce, Naomi Peterson, Minah Radebe, Takalani Radzilani, Heaben Rainers, Sabelo Rasmeni, Doerieyah Reynolds, Noluvo Rode, Surita Roux, Nokwayintombi Scotch, Kate Snyder, Natalie Temmers, Ciska Thompson, Thandokazi Tofile, Nomvuselelo Tshongoyi, Dorothie Van Der Vendt, Christelle Van Niekerk, Monica Vogt, Melissa Wallace, Philippa Woolley, Ntando Yola, Katherine Young

**South Africa: Durban eThekwini site (Centre for AIDS Programme of Research in South Africa):** Diana Chetty, Lorna Dias, Msizi Dladla, Tanuja Gengiah, Magashree Govender, Ishana Harkoo, Shannie Kamal, Mona Kasaval, Isabel Khan, Siphosihle Khanyile, Christina Khwela, Lungile Kubheka, Londiwe Luthuli, Nomusa Mabasa, Bernadette Madlala, Bhavna Maharaj, Nonkululeko Mayisela, Asanda Mdunge, Wendy Mkhize, Avril Mngadi, Atika Moosa, Kalendri Naidoo, Anushka Naidoo, Gonasagrie Nair, Lungani Ndwandwe, Varnika Ramdhani, Joanne Richards, Claudia Shozi, Chandraphrabha Singh, Nompumelelo Zungu

**South Africa: Durban – Botha's Hill, Chatsworth, Isipingo, Tongaat, Umkomaas, Verulam sites (South African Medical Research Council):** Nathlee Abbai, Faeeza Arbee, Amit Ashokumar, Asthi Aungadh, Lindiwe Baba, Sasha Baboolal, Kajal Balkaran, Sivuyisiwe Bebeza,

Hassen Bhayat, Bongiwe Bhengu, Rosemary Bhengu, Bongisile Biyela, Resha Boodhram, Phindile Bulose, Phelelani Buthelezi, Samkelisiwe Buthelezi, Sifiso Buthelezi, Thobekile Buthelezi, Lindiwe Buthelezi, Philisiwe Buthelezi, Lizo Buyeye, Samiksha Byroo, , Samkelisiwe Cebisa, Naureen Cele, Veronica Chamane, Candice Chetty, Keisha Chitray, Phumelele Chonco, Anil Choonilall, Kerusha Chunderduri, Siyabonga Cibane, Shellendra Devnarain, Nischal Dhanpal, Nqubelo Dladla, Duduzile Dlamini, Ethel Dlamini, Nonhlanhla Dubazane, Faith Dube, Cebo Duma, Ziningi Dwayisa, Nkosinathi Faya, Tasneem Gaffoor, Zakir Gaffoor, Rupa Ganesh, Shayhana Ganesh, Sharika Gappoo, Thobile Gasa, Natasha Gounden, Dhevium Govender, Devina Govender, Melissa Govender, Netricia Govender, Shanthie Govender, Vaneshree Govender, Vijayanand Guddera, Phindile Guga, Edith Gumede, Sibusisiwe Gumede, Charlene Harichund, Avika Haridutt, Jeetendra Harilal, Ishina Hemchund, Patricia Hlangu, Thulebona Hlela, Mzophilayo Hlophe, Nivriti Hurbans, Rabia Imamdin, Lakshmi Jagesur, Nitesha Jeenarain, Kaminee Jainarain, Marwah Jenneker, Ayanda Jokozela, Vermala Juggernath, Nirodh Juggessar, Rookaya Kadwa, Duduzile Prudence Khaba, Vincent Khalishwayo, Lungile Khanyile, Nombuso Khanyile, Raphael Khanyile, Mbali Khomo, Norah Khoza, Nonhlanhla Khubone, Ntuthuko Khumalo, Thembinkosi Kleiman Khumalo, Nokukhanya Khuzwayo, Girisha Kistansami, Nothemba Kumalo, Larin Labuschange, Paradise Lembethe, Mbali Mabaso, Sabelo Mabaso, Phumzile Mabusela, Fathima Sayed, Pearl Maduna, Phumzile Magwaza, Rashika Maharaj, Tabita Mahlangeni, Nonhlakanipho Makeka, Nompumelelo Makhanya, , Nkosinathi Makhoba, Lungile Maphumulo, Nonhlanhla Maphumulo, Virginia Mavis Busisiwe Maphumulo, Emmerentia Marx, Nkosinamandla Masinga, Sandile Sydney Mavundla, Thandazile Mbatha, Timothy Mbeje, Mandla Mbeko, Silindile Mbhele, Sandile Mbonambi, Faith Mbuyisa, Michael Mchunu, Nokufika Mchunu, Professor Mdepha, Mduduzi Is Mdletshe, Sihle Meyiwa, Nonthando Mhlaba, Refilwe Mhlongo, Zaselangeni Mhlongo, , Ntombizethu Mkhabela, Lauretta Mkhithi, Lorraine Mkhize, Zinhle Mkhize, Silindile Mkhize, Zaba Mkhize, Thokozani Mkhize, Zwelethu Mkhunyo, Nompumelelo Mkhwanazi, Nompumelelo Mnikathi, Nonzwakazi Mnqonywa, Mbuti Mofokeng., Jayajothi Moodley, Jeeva Moodley, Javanika Moodley, Ramona Moodley, Sharon Moodley, Suri Moonsamy, Neetha Morar, Nonhlanhla Mphili, Innocentia Mpofana, Lindiwe Cecilia Mshibe, Lindumusa Douglas Msomi, Samukelo Msomi, Thabile Msomi, Simakade Msweli, Emmanuel Mthalane, Bongumusa Mthembu, Funeka Mthembu, Thabisile Mthembu, Ntokozo Z Mthethwa, Sicelo Mthimkhulu, Mary-Ignatia Mthlane, Samkelisiwe Mvelase, Goodness Zoh Mvuyane, Lungile Mzimela, Ntokozo Mzimela, Angeline Mzolo, Kumari Naicker, Selvamoney Naicker, Vimla Naicker, Anika Naidoo, Sarita Naidoo, Avashri Naidoo, Ishana Naidoo, Jason Naidoo, Jayganthie Naidoo, Keshani Naidoo, Logashvari Naidoo, , Shereen Naidoo, Sumeshen Naidoo, Nalini Naidu, Alisha Naras, Tashni Nayager, Nombuyiselo Ncayiya, Nonpumeleo Ndaba, Sanele Ndaba, Tholakele Ndala, Pamela Ndamase, Sphindile Ndlovu, Zakhona Ndlovu, James Ndlovu, Senamile Ndlovu, Duduzile Edith Ndwandwe, Khethiwe Joyce Ngobese, Hlengiwe Ngubane, Mduduzi Ngubane, Sibusiso Nhleko, Nishi Nursayhe, Nomfanelo Nxumalo, Khombisile Nyawo, Kerusha Padayachee, Levanya Paramanund, Arendevi Pather, Melanie Perumal, Bathandekile Phahlamohlaka, Jessica Phillip, Jasmin Pillay, Omisha Pillay, Pragasi Pillay, Thotheravani Pillay, Yugashnee Pillay, Anamika Premrajh, Ravendran Punianathan, Luleka Qhogwana, Presha Rajpal, Shiritha Ramdass, Varnika Ramdhani, Gita Ramjee, Nirmala Ramluckan, Sureka Ramnarain, Anand Rampersadh, Renita Ramsumair, Aruna Ratanjee, Meryl Reddy, Melenie Reddy, Neil Reddy, Tharuna Reddy, Vanitha Sakloo, Nosisa Saul, Smangaliso Shangase, Zinhle Shazi, Zilungile Shembe, Zandile Shobede, Samuel Sibisi, Thamsanqwa Sibisi, Zweni Sibiya, Nishanta Singh, Hailey Sithole, Lindiwe Sithole, Samantha Siva, Mandisa Skhosana, , Devarani Soobryan, Elizabeth Spooner, Sizakele Sukazi, Renate Teise, , Tholly Tenza, Themba Tshabalala, Bomkazi Tutshana, Ashvir Udith, Leanne Vallabhjee, Arona Vijay, Hlengiwe Vilakazi, Brenton Viriah, Bhekisisa Wanda, Kubashni Woeber, Thabile Zondi, Thembekile Zulu, Nokuthula Zungu, Phumzile Zungu, Irvin Zwane

**South Africa: Johannesburg site (Wits Reproductive Health and HIV Institute):** Reneilwe Boikanya, Primrose Bojosi, Rutendo Bothma, Busisiwe Cebekhulu, Sarah Cohen, Sinead Delany-Moretlwe, Linh Diep, Clare Dott, Nosipho Gloria Duba, Ntombifuthi Maureen Dube, Portia Ignatia Duma, Livhuwani Millicent Lucia Farisani, Lizzy Gama, Nkgolo Maria Gegana, Nerusha Govender, Sovia Gubayo, Nomsa Gumede, Mikey Parsotham Guness, Marilyn Anne Hoggan, Emily Kekana, Moeketsi David Kgaritsi, Farzana Khan, Themba Langa, Mavis Mantshitseng Madi, Nomfundo Maduno, Pholo Wilson Maenetje, Busisiwe Magazi, Moshukutjoane Lebogang Maila, Kgabo Phineas Makgoka, Bathabile Sithandokuhle Makupula, Nolwazi Nosipho Manzingana, Faith Maputla, Mosidi Calphurnia Maraba, Romeo Martin, Elizabeth Serati Marule, Nombulelo Maseko, Portia Maseko, Nonkululeko Mashabane, Thabang Ephraim Mashiane, Florence Tintswalo Mathebula, Matheus Mathipa, Xolelwa Judy Matikinca, Nkosinathi Vincent Mazibuko, Elizabeth Gugu Mlangeni, Mandla Denis Mlotshwa, Bosisiwe Mnguni, Mampu Modau, Constance Lebohang Modise, Kebuang Mercia Mokgatle, Emelina Tebogo Mokoena, Ann Ophilia Mothle, Magdeline Judith Mthethwa, Emmanuel Sinothi Mthalane, Angeline Doreen Nonhlanhla Mzolo, Elizabeth Nage, Anika Devi Naidoo, Merrilee-Anne Naidoo, Sandy Naidoo, Ishana Naidoo, Nkosinathi Lindela Emmanuel Ncgobo, Duduzile Ethel Ncube, Thembisile Wilmah Ndhlozi, Nontokozo Thandeka Ngcobo, Jonas Ngoetjana, Ringson Ngozo, Lerato Prudence Ngwenya, Dikeledi Nhlapo, Lindelwa Nkangane, Angel Tinny Nyathi, Ogheneruemu Vincent Okwuolise, Thesla Palanee-Phillips, Patricia Pamacheche, Sechaba Tumelo Pitso, Mankwana Pheida Ramafalo, Patience Ramalo, Pranitha Ramchuran, Varnika Ramdhani, Krishnaveni Reddy, Vera Helen Rees, Altaf Sharif, Sylvia Sibongile Sibeko, Siphokazi Sibisi, Wanile Phumzile Sibisi, Vuyane Sizane, Joel Steingo, Reginah Stuurman, Lungiswa Phidelia Thobejane, Lavhelesani Cicilia Tjale, Mpho Tshabalala, Bart Verheyden, Amukelani Califonia Vuma

**Uganda: Kampala site (Makerere University-Johns Hopkins University Research Collaboration):** Dorothy Aanyu, Carolyne Agwau Akello, Prossy Asiimwe, Florence Asiimwe Biira, David Balamusani, James Amos Bazira, Gad Bihabwa, Eleanor Birungi, Steven Bolton, Luke Erasmus Bukenya, Regina Bukenya Nabatanzi, Barbara Bulya Sseguya, Billy Jimmy Busuulwa, Ali Elbireer, Juliane Etima Ongom, Mary Glenn Fowler, Brenda Gati Mirembe, Joseph Ggita, Abraham Juuko, Daniel Kabenge Kizza, Samuel Kabwigu, Bosco Kafufu, Abbey Kafumbe Mukasa, Joshua Kagoda, Brenda Catherine Kakayi, Hadijah Kalule Nabunya, Betty Kamira, Rebecca Kampi, Africano Kamugisha, Justine Kamya, Fred Kapaata Bawulira, Patrick Karugaba, Francis Katongole, Doreen Kemigisha, Beatrice Kiiza, Bonnie King, Kenneth Kintu, Henry Luwugge Sserwadda, Joel Lwanga, Philippa M .Musoke, Henry Makooka, Flavia Matovu Kiweewa, Emmanuel Mayanja, Mary Specioza Mbabali, Dorothy Mirembe, Mahnaz-Oliner Motevalli, Michael Charles Mubiru, Paula Mubiru Namayanja, Magaret Mugenyi, Mary Mukasa Kagwa Najjemba, Mary(Maria) Musisi, Joseph Mutebo, Rosemary Muwawu, Deborah Mwebaza, Joselyne Nabisere, Josephine Nabukeera, Christine Valerie Nagawa Kiwanuka, Susan Najjuka, Clemensia Nakabiito, Susan Nakacwa, Joyce Nakakande, Maria Gorreti Nakalema, Magaret Nakato Saava, Jesca Nakibuka, Teopista Nakyanzi, Justine Nakyeyune, Stella Nalusiba Kalungi, Constance Namirembe, Judith Nampewo, Suzan Nampiira Nkalubo, Sylivia Nankinga, Winnie Nansamba, Stella Nanyonga, Sophie Clare Nanziri, Caroline Nassozi Kawuma, Patrick Ndawula, Monica Nolan, Jane Nsubuga Musisi, Zubayiri Nyanzi, Deo Ogema Wabwire, David Ojok, Francis Onen, Moses Onyuthfua, Sawsan Osman, Carolyne Peris Onyango, Godfrey Rwanzogyera, Rebecca Sakwa, Joseph Semakula, Florence Sempa Kikonyogo, Mark Ssenyonga, Aisha Zalwango

**Zimbabwe: Chitungwiza-Seke South, Chitungwiza-Zengeza, Harare-Spilhaus sites (University of Zimbabwe-University of California San Francisco Collaborative Research**

**Program):** Thembelihle N S Bafana Munatsi, Marvis Banda, Adlight Chandipwisa, Gift T Chareka, Charles Z Chasakara, Tinashe Chidemo, Debra Chigwanha, Emilder Chihota, Sungano Chikono, Anesu Chikonyora, Agnes Chikuni, Zvavahera M Chirenje, Tobias Chitambo, Cathrine Chitsinde, Miria Chitukuta, Trust Chivasa, Patricia M Dhlakama, Lucy Godo, Pardon Gomani, Rodney Goreraza, Norah S Gwete, Kudzai Hlahla, Portia Hunidzarira, Tendai D Hwehwe, Fiona Kachingamire, Cecilia Katanda, Hilary Katema, Terrance Kufakunesu, Margaret Kundeya, Irene Kutinyu, Tarirai Madovi, Tsitsi M Magure, Thecla C Makaya, Rujeko Makoni, Sibongile Makwenda, Loreen Z Mangove, Trace Manyeruke, Annie Mapfunde, Chiedza E C Maponga, Moira Masango, Tapiwa B Masara, Martha Masawi, Shingirayi I Masuko, Angeline Matanhire, Sophia Matenda, Jacob M Matsa, Allen T Matubu, Celia M J Matyanga, Nyaradzo M Mgodi, Felina Mhangami, Erasmus S Mhizha, Margaret Mlingo, Chido T Mlingo, Taina M Motsi, Tariro AM Mpofu, Caroline Mugocha, Faith Mugodhi, Nkhoma Mugowe, Felix G S Muhlanga, Shorai Mukaka, Shedina Mukova, Otillia Munaiwa, Marshall W Munjoma, Marigold Mupunga, Tarisai Murefu, Grant Murewanhema, Petina Musara, Prisca Mutero, Fiona Mutisi, Tariro Muvunzi, Tinaye R L Muzamhindo, Sailas Mwakurudza, Elaine Mwandiwata, Sithabile Ncube, Egifa Ncube, Pepukai Ndadziyira, Grecenia Ndhlovu, Edward Ngwindi, Omega Nyabadza, Sandra Nyakudya, Ennviolata C Nyawera, Fadzai Rimau, Nyaradzo Rupondo, Chenai Rushwaya, Lydia N Samaneka, Berlindah N Shawatu, Rachel Shonhiwa, Thelma T Tauya, Monica Thompson, Christine Vuta, Margret Zinyongo

**Microbicides Trials Network Leadership and Operations Center (University of Pittsburgh & Magee-Womens Research Institute):** Orly Aridor, Linda Bezak, Katherine Bunge, Kim Comer, Ellen Conser, Melissa DeGore, Luis Duran, Maria Foster, Beth Galaska, Sharon Hillier, Cindy Jacobson, Judy Jones, Michelle Leszczewski, Kathy McCarthy, Ian McGowan, Lisa Rossi, Christine Rullo, Devika Singh, Daria Smolinski

**Microbicides Trials Network Leadership and Operations Center – University of Washington:** Jared Baeten, Benjamin Browning-Roberts, Toni Maddox, Deidra Montoya, Kelly Moutsos, Patrick Ndase, Caitlin Scoville

**Microbicides Trials Network Leadership and Operations Center – FHI 360:** Kat Calabrese, Cheryl Cokley, Ashley Mayo, Rachel Scheckter, Katie Schwartz, Kristine Torjesen, Rhonda White

**Microbicides Trials Network Leadership and Operations Center – Population Council:** Irene Friedland, Barbara Mensch, Stan Mierzwa, Samir Souidi, Chung Wu

**Microbicides Trials Network Leadership and Operations Center – RTI International:** Helen Cheng, Miriam Hartmann, Ariana Katz, Nicole Laborde, Jonah Leslie, Alexandra Lutnick, Elizabeth T. Montgomery, Elizabeth Pleasants, Mary Kate Shapley-Quinn, Ariane van der Straten

**Microbicides Trials Network Laboratory Center – Pharmacology Core (Johns Hopkins University):** James Johnson, Craig Hendrix, Madhuri Manohar, Mark Marzinke, Lauren Seserko, Jameson Travers

**Microbicides Trials Network Laboratory Center – Protocol Support Core (Magee-Womens Research Institute):** Michele Austin, Hilary Avolia, May Beamer, Lisa Cosentino, Allison DeMarco, Charlene Dezzutti, Wayne Hall, Sara Hendrickson, Lynda Jones, Edward Livant, Melinda Petrina, Lorna Rabe, Kevin Stoner

**Microbicides Trials Network Laboratory Center – Virology Core (University of Pittsburgh):** Kristen Hamanishi, Krista Eskay, Kelley Gordon, Elias Halvas, Russell Hardesty, John Mellors, Amy Opest, Urvi Parikh, Kerri Penrose

**Microbicides Trials Network Statistical and Data Management Center (Statistical Center for HIV/AIDS Research and Prevention, Fred Hutchinson Cancer Research Center):** Janne Abullarade, Maija Anderson, Jennifer Balkus, Deborah Bassuk, Jen Berthiaume, Joleen Borgerding, Elizabeth Brown, Claire Chapdu, Craig Chin, Missy Cianciola, Cheryl DeBoer, Elaine Dinnie, Martha Doyle, Drew Edwards, Jackie Fitzpatrick, Sharavi Gandham, Haixiao Huang, Marla Husnik, Stacie Kentop, Jenna Krause, Karen Liu, Iraj Mohebalian, Cindy Molitor, Jason Pan, Karen Patterson, Barbra Richardson, Jenn Schille, Katie Snapinn, Daniel Szydlo, Jenny Tseng, Christine Unten, Katie Weaver, Della Wilson

**US National Institutes of Health:** Bola Adedeji**,** Roberta Black, Ronald Barnett, Jane Bupp, Nahida Chakhtoura, Grace Chow, Naana Cleland, Nancy Cogliano, Joanne Csedrik, Carl Dieffenbach, Emily Erbelding, Scharla Estep, Lester Freeman, Donna Germuga, Cynthia Grossman, Judene Hinds, Ana Martinez, Joanne O'Brien, Manizhe Payton, Amy Perez, Jeanna Piper, Dara Potter, Anne Rancourt, Dianne Rausch, Denise Russo, Delta Saint-Vil, Usha Sharma, Rona Siskind, Laura Sivitz Leirman, Lydia E. Soto-Torres, Kathy Stover, Steven Towers, Fulvia Veronese, Sheryl Zwerski

**International Partnership for Microbicides:** Hannelie Carstens, Allison Carter, Tiffany Derrick, Bríd Devlin, Anita Garg, Mariette Malherbe, Winel Mans, Annalene Nel, Jeremy Nuttall, Zeda Rosenberg, Marisa Russell, Euan Seaton, Leonard Solai, Patrick Spence, John Steytler, Neliette van Niekerk, Kathie Windle

**MTN-020/ASPIRE Community Working Group:** Ntokozo Bhengu, Robert Bucklew, Charles Chasakara, Manju Chatani, Cheryl Cokley, Caiphas Dlamini, Thokozani Dlamini, Daniel Gondwe, Phindile Guga, Zerif Kampangire, Milly Katana, Phaleda Kumwenda, Londiwe Luthuli, Vukani Luthuli, Oupa Mafumane, Zethu Mchunu, Wendy Mkhize, Neetha Morar, Emmanuel Mthalane, Thandi Mthiyane, Joanita Muganga, Jason Naidoo, Teopista Nakyanzi, Zodwa Ndlovu, Susan Ngani, Siyabonga Ngqame, Mduduzi Ngubane, Sibusiso Nhleko, Jean Claude Nkebi, Mluleki Nompondwana, Heather Samuels, Bukelwa Sontshatsha, Rhonda White, Tiffanee Wright, Ntando Yola, Amanda Zindela, Fatima Zulu

**MTN-020/ASPIRE Study Monitoring Committee:** Roberta Black, Ward Cates, Connie Celum, Charlene Dezzutti, Deborah Donnell, James Hughes, Sheena McCormack, Lei Wang

| Table S1. Enrollment, by study site | | |
|---|---|---|
| **Country: Site** | **Total Number Screened** | **Total Number Enrolled** |
| Malawi: Blantyre site | 199 | 130 |
| Malawi: Lilongwe site | 200 | 142 |
| South Africa: Cape Town site | 217 | 166 |
| South Africa: Durban – eThekwini site | 736 | 244 |
| South Africa: Durban – Botha's Hill site | 436 | 180 |
| South Africa: Durban – Chatsworth site | 411 | 150 |
| South Africa: Durban – Isipingo site | 314 | 117 |
| South Africa: Durban – Tongaat site | 351 | 103 |
| South Africa: Durban – Umkomaas site | 259 | 103 |
| South Africa: Durban – Verulam site | 346 | 150 |
| South Africa: Johannesburg site | 401 | 213 |
| Uganda: Kampala site | 408 | 253 |
| Zimbabwe: Chitungwiza – Seke South site | 434 | 224 |
| Zimbabwe: Chitungwiza – Zengeza site | 401 | 224 |
| Zimbabwe: Harare – Spilhaus site | 403 | 230 |

| Table S2. | Study inclusion and exclusion criteria |
|---|---|
| **Inclusion Criteria** | Women must have met all of the following criteria to be eligible for inclusion in the study.<br>1) Age 18 through 45 years (inclusive) at screening,<br>2) Able and willing to provide written informed consent to be screened for and to take part in the study<br>3) Able and willing to provide adequate locator information<br>4) HIV uninfected based on testing performed at screening and enrollment<br>5) Per participant report, sexually active, defined as having vaginal intercourse at least once in the 3 months prior to screening<br>6) Using an effective method of contraception at enrollment, and intending to use an effective method for the duration of study participation; effective methods include hormonal methods (except contraceptive rings); intrauterine device (IUD); and sterilization (of participant)<br>7) At screening and enrollment, agrees not to participate in other research studies involving drugs, medical devices, vaginal products, or vaccines for the duration of study participation. *Note: Tampons could be used for the duration of the trial.* |
| **Exclusion Criteria** | Women who met any of the following criteria were excluded from the study.<br>1) Per participant report at screening:<br>a. Intends to become pregnant during study participation<br>b. Plans to relocate away from the study site during study participation<br>c. Plans to travel away from the study site for more than 8 consecutive weeks during study participation<br>2) Pregnant<br>3) Currently breastfeeding<br>4) Diagnosed with urinary tract infection (UTI), unless treated and symptoms are resolved prior to enrollment<br>5) Diagnosed with pelvic inflammatory disease, an STI or reproductive tract infection requiring treatment per current WHO guidelines, unless treated and symptoms are resolved prior to enrollment<br>6) Has a clinically apparent Grade 2 or higher pelvic exam finding. Cervical bleeding associated with speculum insertion and/or specimen collection judged to be within the range of normal is not exclusionary.<br>7) Participant report and/or clinical evidence of any of the following:<br>a. Known adverse reaction to any of the study products (ever)<br>b. Known adverse reaction to latex (ever)<br>c. Chronic vaginal candidiasis<br>d. Non-therapeutic injection drug use in the 12 months prior to Screening<br>e. Post-exposure prophylaxis (PEP) for HIV-1 exposure within 6 months prior to enrollment<br>f. Last pregnancy outcome 90 days or less prior to enrollment<br>g. Gynecologic or genital procedure (e.g., tubal ligation, dilation and curettage, piercing) 90 days or less prior to enrollment<br>h. Participation in any other research study involving drugs, medical devices, vaginal products, or vaccines, within 60 days of enrollment<br>i. Participation in any HIV prevention study using systemic or topical antiretroviral medications, within 12 months of enrollment<br>j. As determined by the site investigator, any significant uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease, including active tuberculosis<br>8) Has any of the following laboratory abnormalities at Screening Visit:<br>a. Aspartate aminotransferase (AST) or alanine transaminase (ALT) Grade 1 or higher<br>b. Creatinine Grade 2 or higher<br>c. Hemoglobin Grade 2 or higher<br>d. Platelet count Grade 1 or higher<br>e. Pap result Grade 2 or higher<br>9) Has any other condition that, in the opinion of the site investigator, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives |

| Table S3. Site Institutional Review Boards/Ethics Committees | |
|---|---|
| **Country: Site** | **Institutional Review Board / Ethics Committee** |
| Malawi: Blantyre site | National Health Sciences Research Committee of Malawi<br>Johns Hopkins University Bloomberg School of Public Health Institutional Review Board |
| Malawi: Lilongwe site | National Health Sciences Research Committee of Malawi<br>University of North Carolina at Chapel Hill Institutional Review Board |
| South Africa: Cape Town site | University of Cape Town: Human Research Ethics Committee |
| South Africa: Durban – eThekwini site | Biomedical Research Ethics Committee, University of KwaZulu-Natal |
| South Africa: Durban – Botha's Hill site | South African Medical Research Council Ethics Committee |
| South Africa: Durban – Chatsworth site | South African Medical Research Council Ethics Committee |
| South Africa: Durban – Isipingo site | South African Medical Research Council Ethics Committee |
| South Africa: Durban – Tongaat site | South African Medical Research Council Ethics Committee |
| South Africa: Durban – Umkomaas site | South African Medical Research Council Ethics Committee |
| South Africa: Durban – Verulam site | South African Medical Research Council Ethics Committee |
| South Africa: Johannesburg site | Wits Human Research Ethics Committee, University of Witwatersrand |
| Uganda: Kampala site | Joint Clinical Research Centre Institutional Review Board<br>Johns Hopkins University School of Medicine Institutional Review Board |
| Zimbabwe: Chitungwiza – Seke South site | Medical Research Council of Zimbabwe<br>Committee on Human Research, University of California - San Francisco |
| Zimbabwe: Chitungwiza – Zengeza site | Medical Research Council of Zimbabwe<br>Committee on Human Research, University of California - San Francisco |
| Zimbabwe: Harare – Spilhaus site | Medical Research Council of Zimbabwe<br>Committee on Human Research, University of California - San Francisco |

**Table S4. Study visits and procedures**

| | | SCR | ENR | Monthly Visits | Quarterly Visits | Semi-Annual Visits | PUEV** | Study Exit/ Term. Visit |
|---|---|---|---|---|---|---|---|---|
| **ADMINISTRATIVE AND REGULATORY** | | | | | | | | |
| Obtain informed consent | | X | X | | | | | |
| Assign a unique Participant Identification (PTID) number | | X | | | | | | |
| Assess and/or confirm eligibility | | X | X | | | | | |
| Collect/review/update locator information | | X | X | X | X | X | X | X |
| Randomization | | | X | | | | | |
| Provide reimbursement | | X | X | X | X | X | X | X |
| Schedule next visit | | * | X | X | X | X | X | * |
| **BEHAVIORAL** | | | | | | | | |
| Contraceptive counseling | | X | X | X | X | X | | |
| Protocol adherence, including VR adherence counseling | | | X | X | X | X | | |
| HIV/STI risk reduction counseling | | X | X | X | X | X | X | X |
| HIV pre- and post-test counseling | | X | X | X | X | X | X | X |
| Conduct a behavioral assessment includes sexual activity, condom use, and intravaginal practices | | | X | | X | X | X | X |
| Conduct an adherence assessment | | | | X | X | X | X | |
| Conduct an acceptability assessment | | | | | X | X | X | |
| Conduct social harms assessment | | | | | X | X | X | |
| **CLINICAL** | | | | | | | | |
| Obtain/update medical and menstrual history | | X | X | X | X | X | X | X |
| Obtain/update concomitant medications | | X | X | X | X | X | X | X |
| Conduct a physical examination | | X | X | * | X | X | X | |
| Perform a pelvic exam | | X | *₸ | *₸ | *₸ | X | X | *₸ |
| Prescribe contraceptives | | * | * | * | * | * | * | * |
| Disclose available test results | | | X | X | X | X | X | X |
| Record/update AEs | | | | X | X | X | X | X |
| Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings | | * | * | * | * | * | * | * |
| **LABORATORY** | | | | | | | | |
| URINE | hCG | X | X | X | X | X | X | X |
| URINE | Urine culture | * | * | * | * | * | * | * |
| URINE | NAAT for GC/CT | X | * | * | * | X | * | * |
| BLOOD | HIV-1 Serology | X | X | X | X | X | X | X |
| BLOOD | CBC with platelets | X | | | X | X | X | |
| BLOOD | Chemistries | X | | | X | X | X | |
| BLOOD | Syphilis serology | X | | * | * | * | X | |
| BLOOD | Plasma | | ◊ | | X | X | X | X |
| PELVIC | Study VR adherence assessment(s) | | | * | * | * | * | |
| PELVIC | Rapid test for Trichomonas | X | *₸ | *₸ | *₸ | X | *₸ | *₸ |
| PELVIC | Herpes lesion testing | *₸ | *₸ | *₸ | *₸ | *₸ | *₸ | *₸ |
| PELVIC | Vaginal fluid pH | X₸ | *₸ | *₸ | *₸ | X | X | *₸ |
| PELVIC | KOH wet mount for candidiasis | *₸ | *₸ | *₸ | *₸ | *₸ | *₸ | *₸ |
| PELVIC | Saline wet mount for BV | *₸ | *₸ | *₸ | *₸ | *₸ | *₸ | *₸ |
| PELVIC | Gram stain | X | | | | X | X | |
| PELVIC | Vaginal fluid | | X | X | X | X | X | X |
| PELVIC | Pap Smear interpretation | * | | | | | X | |
| PELVIC | Endocervical swab | X | | | | X | X | |
| **STUDY PRODUCT/ SUPPLIES** | | | | | | | | |
| Provision of study specified condoms | | X | X | X | X | X | X | X |
| Provision of study VR instructions | | | X | * | * | * | | |
| Provision of one study VR for insertion | | | X | X | X | X | | |
| Participant or clinician/designee to remove used study VR | | | | X | X | X | X | |
| Digital exam(s) by clinician to check VR placement | | | X | ₪ * | * | * | | |
| Demonstrated attempt to remove and reinsert the ring | | | X | | | | | |
| Collection of used study VR | | | | X | X | X | X | |
| Dispense a bottle of water, at select sites | | | * | * | * | * | | |

X mandatory, * If indicated, ₸ per local standard of care, ◊= for archive, ₪= required at Month 1, **= When the PUEV coincides with the timing of a Semi-Annual Visit (Months 6, 12, 18, etc.), all procedures except for the provision of study product and related procedures will be conducted

**Table S5. Statistical design and analysis approach**

The trial was designed with 90% power to detect a 60% reduction in risk of HIV-1 infection, with a one-sided alpha of 0.025. Like other trials of novel HIV-1 prevention interventions, the trial was powered so that lower bound of the 95% confidence interval, if the reduction in HIV-1 achieved 60%, would exclude a 25% reduction in risk.

This use of a non-zero null hypothesis for power calculations was done for several reasons. First, some in the field have argued results would garner greater confidence by public health policymakers for later implementation if interventions were demonstrated to have effects that were definitively separate from zero. Second, if behavioral disinhibition or other factors that might undermine HIV-1 protection effectiveness in real-world settings were to occur, then products with higher HIV-1 protection estimates in clinical trials may have some cushion for implementation. Third, when this trial was designed it was to be the only phase III trial of this product, and thus, for regulatory reasons a more strongly powered study was desired – specifically, if a single pivotal trial is planned, then its power must be greater than that of a single well-powered trial (for US FDA requirements, at least one and one-half times the power of a single trial); one way to achieve that additional power is to have a non-zero null and to conduct interim monitoring of effectiveness against that non-zero null (thus ensuring that the trial would not stop too early for too small of an effect that would not as a single trial meet regulatory guidelines).

However, several features of the study and developments in the field contributed to the analysis plan for the present study. First, from its inception, the statistical plan for this trial anticipated a primary analysis against a standard null of zero, with secondary analyses done against the non-zero null. Consistent with this approach, interim monitoring for futility in the trial was against a null of zero, not against a null of 25%. Second, after this trial was designed, The Ring Study, a second evaluation of the dapivirine vaginal ring, was expanded from an extended phase II study to be a phase III study. The design of the present study was not changed, but the regulatory plan to consider only one pivotal trial for HIV-1 protection effects was modified to include both studies. Finally, other trials in this field that have been designed with non-zero null effects have presented their primary findings against the standard zero null – defined in the table below. The iPrEx example is particularly important. That trial was designed against a non-zero null of 30%, but it failed to rule out that effect in its primary analysis (its lower bound of

the 95% confidence interval was 15%). However, in combination with other data from the field, it served as a pivotal study for the regulatory approval and normative guidance regarding combination emtricitabine/tenofovir disoproxil fumarate as daily oral pre-exposure prophylaxis against HIV-1 acquisition.

| **Table S5. Prior placebo-controlled phase IIB/III studies of HIV-1 antiretroviral prophylaxis: null hypothesis for design and for primary analysis** | | | |
|---|---|---|---|
| ***Study*** | **Null hypothesis for design** | **Null hypothesis for primary analysis** | **Final HIV-1 protection effectiveness estimate (95% CI)** |
| **IPERGAY**[1] | 0% | 0% | 86% (40, 98) |
| **Partners PrEP Study**[2]***** | 30% | 0% | 75% (55, 87) |
| **TDF2**[3] | 10% | 0% | 62% (22, 83) |
| **BTS**[4] | 10% | 0% | 49% (10,72) |
| **iPrEx**[5] | 30% | 0% | 44% (15,63) |
| **FEM-PrEP**[6] | 25% | 0% | 6% (-52, 41) |
| **VOICE**[7]***** | 25% | 0% | -4% (-49, 27) |
| **CAPRISA 004**[8] | 0% | 0% | 39% (6,60) |
| **FACTS 001**[9] | 0% | 0% | 0% (-40,30) |

* For the Partners PrEP Study and VOICE, where more than one active arm was tested, only the oral emtricitabine/tenofovir disoproxil fumarate pill effectiveness estimate is provided, as an example.

**Table S6. Primary safety events, detailed listing**

The primary safety endpoint for the study was defined as a composite of any serious adverse event, any death, any Grade 3 and 4 adverse events, and any Grade 2 adverse event assessed by the study clinicians as related to the study product. Table S6 presents all primary safety events by type of adverse event, treatment group, grade, and relatedness assessment: serious adverse events (Table S6a), deaths (Table S6b), Grade 4 events (Table S6c), Grade 3 events (Table S6d), and Grade 2 events assessed as related (Table S6e). Serious adverse events would encompass the deaths as well as any of the other primary safety events deemed to be serious, and thus there is duplication between Table S6a and some parts of the other tables.

**Table S6a. Serious adverse events (page 1 of 14)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Participants with Serious AEs** | | | |
| Not Related | 48 (3.6%) | 52 (4.0%) | 100 (3.8%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 48 (3.6%) | 52 (4.0%) | 100 (3.8%) |
| **Blood and lymphatic system disorders** | | | |
| Hypochromic anaemia | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| **Congenital, familial and genetic disorders** | | | |
| Arnold-Chiari malformation | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Congenital anomaly in offspring | | | |
| Not Related | 2 (0.2%) | 5 (0.4%) | 7 (0.3%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 2 (0.2%) | 5 (0.4%) | 7 (0.3%) |
| **Gastrointestinal disorders** | | | |
| Abdominal pain | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |

**Table S6a. Serious adverse events (page 2 of 14)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Gastrointestinal disorders (continued)** | | | |
| Abdominal pain upper | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Diarrhoea | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Gastritis | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Umbilical hernia | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| **General disorders and administration site conditions** | | | |
| Oedema peripheral | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Pyrexia | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |

**Table S6a. Serious adverse events (page 3 of 14)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Hepatobiliary disorders** | | | |
| Cholecystitis | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Cholecystitis acute | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Cholelithiasis | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| **Immune system disorders** | | | |
| Anaphylactic shock | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| **Infections and infestations** | | | |
| Abscess limb | | | |
| Not Related | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |

**Table S6a. Serious adverse events (page 4 of 14)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Infections and infestations (continued)** | | | |
| Appendicitis | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Bartholin's abscess | | | |
| Not Related | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Cellulitis | | | |
| Not Related | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Cervicitis | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Dysentery | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Gastroenteritis | | | |
| Not Related | 2 (0.2%) | 0 (0.0%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 2 (0.2%) | 0 (0.0%) | 2 (0.1%) |

**Table S6a. Serious adverse events (page 5 of 14)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Infections and infestations (continued)** | | | |
| Infected bites | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Lower respiratory tract infection | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Malaria | | | |
| Not Related | 2 (0.2%) | 3 (0.2%) | 5 (0.2%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 2 (0.2%) | 3 (0.2%) | 5 (0.2%) |
| Meningitis tuberculous | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Pelvic inflammatory disease | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Peritonsillar abscess | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |

**Table S6a. Serious adverse events (page 6 of 14)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Infections and infestations (continued)** | | | |
| Pneumonia | | | |
| Not Related | 2 (0.2%) | 0 (0.0%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 2 (0.2%) | 0 (0.0%) | 2 (0.1%) |
| Postpartum sepsis | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Pulmonary tuberculosis | | | |
| Not Related | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Subcutaneous abscess | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Tuberculosis | | | |
| Not Related | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Tuberculosis gastrointestinal | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |

**Table S6a. Serious adverse events (page 7 of 14)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Infections and infestations (continued)** | | | |
| Upper respiratory tract infection | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Urinary tract infection | | | |
| Not Related | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Viral infection | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Wound infection | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| **Injury, poisoning and procedural complications** | | | |
| Abdominal injury | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Ankle fracture | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |

**Table S6a. Serious adverse events (page 8 of 14)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Injury, poisoning and procedural complications (continued)** | | | |
| Back injury | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Burns first degree | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Face injury | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Fibula fracture | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Head injury | | | |
| Not Related | 2 (0.2%) | 1 (0.1%) | 3 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 2 (0.2%) | 1 (0.1%) | 3 (0.1%) |
| Joint dislocation | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |

**Table S6a. Serious adverse events (page 9 of 14)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Injury, poisoning and procedural complications (continued)** | | | |
| Laceration | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Limb injury | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Lower limb fracture | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Procedural pain | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Snake bite | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Stab wound | | | |
| Not Related | 2 (0.2%) | 2 (0.2%) | 4 (0.2%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 2 (0.2%) | 2 (0.2%) | 4 (0.2%) |

**Table S6a. Serious adverse events (page 10 of 14)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Injury, poisoning and procedural complications (continued)** | | | |
| Thermal burn | | | |
| Not Related | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| **Investigations** | | | |
| Aspartate aminotransferase increased | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Platelet count decreased | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| **Metabolism and nutrition disorders** | | | |
| Diabetes mellitus | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| **Nervous system disorders** | | | |
| Cerebrovascular accident | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |

**Table S6a. Serious adverse events (page 11 of 14)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Nervous system disorders (continued)** | | | |
| Epilepsy | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Headache | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Hepatic encephalopathy | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Seizure | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| **Pregnancy, puerperium and perinatal conditions** | | | |
| Post abortion haemorrhage | | | |
| Not Related | 4 (0.3%) | 6 (0.5%) | 10 (0.4%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 4 (0.3%) | 6 (0.5%) | 10 (0.4%) |
| Premature labour | | | |
| Not Related | 1 (0.1%) | 2 (0.2%) | 3 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 2 (0.2%) | 3 (0.1%) |

**Table S6a. Serious adverse events (page 12 of 14)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Pregnancy, puerperium and perinatal conditions (continued)** | | | |
| Ruptured ectopic pregnancy | | | |
| Not Related | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| **Psychiatric disorders** | | | |
| Bipolar disorder | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Confusional state | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Depression | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Intentional self-injury | | | |
| Not Related | 2 (0.2%) | 2 (0.2%) | 4 (0.2%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 2 (0.2%) | 2 (0.2%) | 4 (0.2%) |
| Mania | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |

**Table S6a. Serious adverse events (page 13 of 14)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Psychiatric disorders (continued)** | | | |
| Suicidal ideation | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Suicide attempt | | | |
| Not Related | 1 (0.1%) | 2 (0.2%) | 3 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 2 (0.2%) | 3 (0.1%) |
| **Reproductive system and breast disorders** | | | |
| Adnexa uteri cyst | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Adnexa uteri mass | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Metrorrhagia | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Ovarian cyst | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |

**Table S6a. Serious adverse events (page 14 of 14)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Dyspnoea | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Pulmonary embolism | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| **Skin and subcutaneous tissue disorders** | | | |
| Lipohypertrophy | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| **Vascular disorders** | | | |
| Hypertension | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |

**Table S6b. Deaths (page 1 of 1)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Participants with Grade 5 AEs** | | | |
| Not Related | 3 (0.2%) | 4 (0.3%) | 7 (0.3%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 3 (0.2%) | 4 (0.3%) | 7 (0.3%) |
| **Infections and infestations** | | | |
| Pulmonary tuberculosis | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Tuberculosis gastrointestinal | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| **Injury, poisoning and procedural complications** | | | |
| Abdominal injury | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Stab wound | | | |
| Not Related | 1 (0.1%) | 2 (0.2%) | 3 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 2 (0.2%) | 3 (0.1%) |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Pulmonary embolism | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |

**Table S6c. Grade 4 events (page 1 of 7)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Participants with Grade 4 AEs** | | | |
| Not Related | 23 (1.7%) | 22 (1.7%) | 45 (1.7%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 23 (1.7%) | 22 (1.7%) | 45 (1.7%) |
| **Blood and lymphatic system disorders** | | | |
| Hypochromic anaemia | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Neutropenia | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Thrombocytopenia | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| **Congenital, familial and genetic disorders** | | | |
| Arnold-Chiari malformation | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |

**Table S6c. Grade 4 events (page 2 of 7)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Gastrointestinal disorders** | | | |
| Abdominal pain upper | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| **Hepatobiliary disorders** | | | |
| Liver disorder | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| **Immune system disorders** | | | |
| Anaphylactic shock | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| **Infections and infestations** | | | |
| Acute hepatitis B | | | |
| Not Related | 0 (0.0%) | 3 (0.2%) | 3 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 3 (0.2%) | 3 (0.1%) |
| Dysentery | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |

**Table S6c. Grade 4 events (page 3 of 7)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Infections and infestations (continued)** | | | |
| Malaria | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Meningitis tuberculous | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Postpartum sepsis | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| **Injury, poisoning and procedural complications** | | | |
| Alcohol poisoning | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Stab wound | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |

**Table S6c. Grade 4 events (page 4 of 7)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Investigations** | | | |
| Alanine aminotransferase increased | | | |
| Not Related | 3 (0.2%) | 1 (0.1%) | 4 (0.2%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 3 (0.2%) | 1 (0.1%) | 4 (0.2%) |
| Aspartate aminotransferase increased | | | |
| Not Related | 1 (0.1%) | 2 (0.2%) | 3 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 2 (0.2%) | 3 (0.1%) |
| Lymphocyte count decreased | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Platelet count decreased | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| **Metabolism and nutrition disorders** | | | |
| Abnormal loss of weight | | | |
| Not Related | 2 (0.2%) | 2 (0.2%) | 4 (0.2%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 2 (0.2%) | 2 (0.2%) | 4 (0.2%) |

**Table S6c. Grade 4 events (page 5 of 7)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Nervous system disorders** | | | |
| Cerebrovascular accident | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Epilepsy | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| **Pregnancy, puerperium and perinatal conditions** | | | |
| Post abortion haemorrhage | | | |
| Not Related | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Premature labour | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Ruptured ectopic pregnancy | | | |
| Not Related | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |

**Table S6c. Grade 4 events (page 6 of 7)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Psychiatric disorders** | | | |
| Bipolar disorder | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Depression | | | |
| Not Related | 2 (0.2%) | 0 (0.0%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 2 (0.2%) | 0 (0.0%) | 2 (0.1%) |
| Intentional self-injury | | | |
| Not Related | 2 (0.2%) | 2 (0.2%) | 4 (0.2%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 2 (0.2%) | 2 (0.2%) | 4 (0.2%) |
| Suicidal ideation | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Suicide attempt | | | |
| Not Related | 1 (0.1%) | 2 (0.2%) | 3 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 2 (0.2%) | 3 (0.1%) |
| **Reproductive system and breast disorders** | | | |
| Metrorrhagia | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |

**Table S6c. Grade 4 events (page 7 of 7)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Vascular disorders** | | | |
| Hypertension | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |

**Table S6d. Grade 3 events (page 1 of 19)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n | (%) | Dapivirine (N=1313) n | (%) | Total (N=2629) n | (%) |
|---|---|---|---|---|---|---|
| **Participants with Grade 3 AEs** | | | | | | |
| Not Related | 162 | (12.3%) | 151 | (11.5%) | 313 | (11.9%) |
| Related | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) |
| Total | 162 | (12.3%) | 151 | (11.5%) | 313 | (11.9%) |
| **Blood and lymphatic system disorders** | | | | | | |
| Anaemia | | | | | | |
| Not Related | 1 | (0.1%) | 6 | (0.5%) | 7 | (0.3%) |
| Related | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) |
| Total | 1 | (0.1%) | 6 | (0.5%) | 7 | (0.3%) |
| Anaemia of pregnancy | | | | | | |
| Not Related | 2 | (0.2%) | 0 | (0.0%) | 2 | (0.1%) |
| Related | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) |
| Total | 2 | (0.2%) | 0 | (0.0%) | 2 | (0.1%) |
| Hypochromic anaemia | | | | | | |
| Not Related | 1 | (0.1%) | 1 | (0.1%) | 2 | (0.1%) |
| Related | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) |
| Total | 1 | (0.1%) | 1 | (0.1%) | 2 | (0.1%) |
| Lymphopenia | | | | | | |
| Not Related | 1 | (0.1%) | 0 | (0.0%) | 1 | (<.1%) |
| Related | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) |
| Total | 1 | (0.1%) | 0 | (0.0%) | 1 | (<.1%) |
| Microcytic anaemia | | | | | | |
| Not Related | 1 | (0.1%) | 0 | (0.0%) | 1 | (<.1%) |
| Related | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) |
| Total | 1 | (0.1%) | 0 | (0.0%) | 1 | (<.1%) |

**Table S6d. Grade 3 events (page 2 of 19)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Blood and lymphatic system disorders (continued)** | | | |
| Neutropenia | | | |
| Not Related | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Thrombocytopenia | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| **Cardiac disorders** | | | |
| Cardiac disorder | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| **Congenital, familial and genetic disorders** | | | |
| Congenital anomaly in offspring | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| **Gastrointestinal disorders** | | | |
| Abdominal pain | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |

**Table S6d. Grade 3 events (page 3 of 19)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Gastrointestinal disorders (continued)** | | | |
| Diarrhoea | | | |
| Not Related | 2 (0.2%) | 1 (0.1%) | 3 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 2 (0.2%) | 1 (0.1%) | 3 (0.1%) |
| Diarrhoea haemorrhagic | | | |
| Not Related | 2 (0.2%) | 0 (0.0%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 2 (0.2%) | 0 (0.0%) | 2 (0.1%) |
| Gastritis | | | |
| Not Related | 3 (0.2%) | 0 (0.0%) | 3 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 3 (0.2%) | 0 (0.0%) | 3 (0.1%) |
| Nausea | | | |
| Not Related | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Peptic ulcer | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Toothache | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |

**Table S6d. Grade 3 events (page 4 of 19)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **General disorders and administration site conditions** | | | |
| Asthenia | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Oedema peripheral | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Pyrexia | | | |
| Not Related | 2 (0.2%) | 1 (0.1%) | 3 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 2 (0.2%) | 1 (0.1%) | 3 (0.1%) |
| **Hepatobiliary disorders** | | | |
| Cholecystitis | | | |
| Not Related | 2 (0.2%) | 0 (0.0%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 2 (0.2%) | 0 (0.0%) | 2 (0.1%) |
| Cholecystitis acute | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Cholelithiasis | | | |
| Not Related | 1 (0.1%) | 2 (0.2%) | 3 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 2 (0.2%) | 3 (0.1%) |

**Table S6d. Grade 3 events (page 5 of 19)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Immune system disorders** | | | |
| Hypersensitivity | | | |
| Not Related | 2 (0.2%) | 1 (0.1%) | 3 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 2 (0.2%) | 1 (0.1%) | 3 (0.1%) |
| **Infections and infestations** | | | |
| Abscess limb | | | |
| Not Related | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Acute HIV infection | | | |
| Not Related | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Appendicitis | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Bartholin's abscess | | | |
| Not Related | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Cellulitis | | | |
| Not Related | 1 (0.1%) | 2 (0.2%) | 3 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 2 (0.2%) | 3 (0.1%) |

**Table S6d. Grade 3 events (page 6 of 19)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Infections and infestations (continued)** | | | |
| Dermatitis infected | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Diarrhoea infectious | | | |
| Not Related | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Gastroenteritis | | | |
| Not Related | 5 (0.4%) | 7 (0.5%) | 12 (0.5%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 5 (0.4%) | 7 (0.5%) | 12 (0.5%) |
| Genitourinary chlamydia infection | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Genitourinary tract gonococcal infection | | | |
| Not Related | 6 (0.5%) | 4 (0.3%) | 10 (0.4%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 6 (0.5%) | 4 (0.3%) | 10 (0.4%) |
| Helminthic infection | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |

**Table S6d. Grade 3 events (page 7 of 19)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Infections and infestations (continued)** | | | |
| Herpes zoster | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Infected bites | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Influenza | | | |
| Not Related | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Lower respiratory tract infection | | | |
| Not Related | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Malaria | | | |
| Not Related | 5 (0.4%) | 4 (0.3%) | 9 (0.3%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 5 (0.4%) | 4 (0.3%) | 9 (0.3%) |
| Pelvic inflammatory disease | | | |
| Not Related | 2 (0.2%) | 2 (0.2%) | 4 (0.2%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 2 (0.2%) | 2 (0.2%) | 4 (0.2%) |

**Table S6d. Grade 3 events (page 8 of 19)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Infections and infestations (continued)** | | | |
| Peritonsillar abscess | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Pneumonia | | | |
| Not Related | 2 (0.2%) | 1 (0.1%) | 3 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 2 (0.2%) | 1 (0.1%) | 3 (0.1%) |
| Pulmonary tuberculosis | | | |
| Not Related | 2 (0.2%) | 2 (0.2%) | 4 (0.2%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 2 (0.2%) | 2 (0.2%) | 4 (0.2%) |
| Pyelonephritis | | | |
| Not Related | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Sinusitis | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Subcutaneous abscess | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |

**Table S6d. Grade 3 events (page 9 of 19)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Infections and infestations (continued)** | | | |
| Tonsillitis | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Tuberculosis | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Upper respiratory tract infection | | | |
| Not Related | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Urinary tract infection | | | |
| Not Related | 1 (0.1%) | 3 (0.2%) | 4 (0.2%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 3 (0.2%) | 4 (0.2%) |
| Viral infection | | | |
| Not Related | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Wound infection | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |

**Table S6d. Grade 3 events (page 10 of 19)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Injury, poisoning and procedural complications** | | | |
| Ankle fracture | | | |
| Not Related | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Back injury | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Face injury | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Fibula fracture | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Head injury | | | |
| Not Related | 3 (0.2%) | 2 (0.2%) | 5 (0.2%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 3 (0.2%) | 2 (0.2%) | 5 (0.2%) |
| Joint dislocation | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |

**Table S6d. Grade 3 events (page 11 of 19)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Injury, poisoning and procedural complications (continued)** | | | |
| Laceration | | | |
| Not Related | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Limb injury | | | |
| Not Related | 2 (0.2%) | 0 (0.0%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 2 (0.2%) | 0 (0.0%) | 2 (0.1%) |
| Lower limb fracture | | | |
| Not Related | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Procedural pain | | | |
| Not Related | 3 (0.2%) | 0 (0.0%) | 3 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 3 (0.2%) | 0 (0.0%) | 3 (0.1%) |
| Skin abrasion | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Snake bite | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |

**Table S6d. Grade 3 events (page 12 of 19)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Injury, poisoning and procedural complications (continued)** | | | |
| Soft tissue injury | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Stab wound | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Thermal burn | | | |
| Not Related | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Wrist fracture | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| **Investigations** | | | |
| Alanine aminotransferase increased | | | |
| Not Related | 6 (0.5%) | 6 (0.5%) | 12 (0.5%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 6 (0.5%) | 6 (0.5%) | 12 (0.5%) |
| Aspartate aminotransferase increased | | | |
| Not Related | 4 (0.3%) | 7 (0.5%) | 11 (0.4%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 4 (0.3%) | 7 (0.5%) | 11 (0.4%) |

**Table S6d. Grade 3 events (page 13 of 19)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Investigations (continued)** | | | |
| Blood bilirubin increased | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Blood pressure increased | | | |
| Not Related | 3 (0.2%) | 4 (0.3%) | 7 (0.3%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 3 (0.2%) | 4 (0.3%) | 7 (0.3%) |
| Haemoglobin decreased | | | |
| Not Related | 6 (0.5%) | 5 (0.4%) | 11 (0.4%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 6 (0.5%) | 5 (0.4%) | 11 (0.4%) |
| Lymphocyte count decreased | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Neutrophil count decreased | | | |
| Not Related | 5 (0.4%) | 7 (0.5%) | 12 (0.5%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 5 (0.4%) | 7 (0.5%) | 12 (0.5%) |
| Platelet count decreased | | | |
| Not Related | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |

**Table S6d. Grade 3 events (page 14 of 19)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Metabolism and nutrition disorders** | | | |
| Abnormal loss of weight | | | |
| Not Related | 51 (3.9%) | 41 (3.1%) | 92 (3.5%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 51 (3.9%) | 41 (3.1%) | 92 (3.5%) |
| Decreased appetite | | | |
| Not Related | 10 (0.8%) | 8 (0.6%) | 18 (0.7%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 10 (0.8%) | 8 (0.6%) | 18 (0.7%) |
| Diabetes mellitus | | | |
| Not Related | 5 (0.4%) | 1 (0.1%) | 6 (0.2%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 5 (0.4%) | 1 (0.1%) | 6 (0.2%) |
| Type 2 diabetes mellitus | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| **Musculoskeletal and connective tissue disorders** | | | |
| Back pain | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Musculoskeletal pain | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |

**Table S6d. Grade 3 events (page 15 of 19)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Nervous system disorders** | | | |
| Dizziness | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Generalised tonic-clonic seizure | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Headache | | | |
| Not Related | 3 (0.2%) | 2 (0.2%) | 5 (0.2%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 3 (0.2%) | 2 (0.2%) | 5 (0.2%) |
| Hepatic encephalopathy | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Seizure | | | |
| Not Related | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| **Pregnancy, puerperium and perinatal conditions** | | | |
| Cephalo-pelvic disproportion | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |

**Table S6d. Grade 3 events (page 16 of 19)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n | (%) | Dapivirine (N=1313) n | (%) | Total (N=2629) n | (%) |
|---|---|---|---|---|---|---|
| **Pregnancy, puerperium and perinatal conditions (continued)** | | | | | | |
| Post abortion haemorrhage | | | | | | |
| Not Related | 4 | (0.3%) | 5 | (0.4%) | 9 | (0.3%) |
| Related | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) |
| Total | 4 | (0.3%) | 5 | (0.4%) | 9 | (0.3%) |
| Premature labour | | | | | | |
| Not Related | 1 | (0.1%) | 0 | (0.0%) | 1 | (<.1%) |
| Related | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) |
| Total | 1 | (0.1%) | 0 | (0.0%) | 1 | (<.1%) |
| Vomiting in pregnancy | | | | | | |
| Not Related | 1 | (0.1%) | 1 | (0.1%) | 2 | (0.1%) |
| Related | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) |
| Total | 1 | (0.1%) | 1 | (0.1%) | 2 | (0.1%) |
| **Psychiatric disorders** | | | | | | |
| Depressed mood | | | | | | |
| Not Related | 1 | (0.1%) | 0 | (0.0%) | 1 | (<.1%) |
| Related | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) |
| Total | 1 | (0.1%) | 0 | (0.0%) | 1 | (<.1%) |
| Major depression | | | | | | |
| Not Related | 1 | (0.1%) | 0 | (0.0%) | 1 | (<.1%) |
| Related | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) |
| Total | 1 | (0.1%) | 0 | (0.0%) | 1 | (<.1%) |
| Mood altered | | | | | | |
| Not Related | 1 | (0.1%) | 0 | (0.0%) | 1 | (<.1%) |
| Related | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) |
| Total | 1 | (0.1%) | 0 | (0.0%) | 1 | (<.1%) |

**Table S6d. Grade 3 events (page 17 of 19)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Reproductive system and breast disorders** | | | |
| Adnexa uteri cyst | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Adnexa uteri mass | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Cervical dysplasia | | | |
| Not Related | 1 (0.1%) | 3 (0.2%) | 4 (0.2%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 3 (0.2%) | 4 (0.2%) |
| Coital bleeding | | | |
| Not Related | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 2 (0.2%) | 2 (0.1%) |
| Dysmenorrhoea | | | |
| Not Related | 2 (0.2%) | 2 (0.2%) | 4 (0.2%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 2 (0.2%) | 2 (0.2%) | 4 (0.2%) |
| Menorrhagia | | | |
| Not Related | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |

**Table S6d. Grade 3 events (page 18 of 19)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Reproductive system and breast disorders (continued)** | | | |
| Metrorrhagia | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Ovarian cyst | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Pelvic pain | | | |
| Not Related | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 1 (0.1%) | 2 (0.1%) |
| Perineal ulceration | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Dyspnoea | | | |
| Not Related | 2 (0.2%) | 0 (0.0%) | 2 (0.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 2 (0.2%) | 0 (0.0%) | 2 (0.1%) |
| Epistaxis | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |

**Table S6d. Grade 3 events (page 19 of 19)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Skin and subcutaneous tissue disorders** | | | |
| Lipohypertrophy | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Rash maculo-papular | | | |
| Not Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Skin ulcer | | | |
| Not Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| **Vascular disorders** | | | |
| Hypertension | | | |
| Not Related | 5 (0.4%) | 0 (0.0%) | 5 (0.2%) |
| Related | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Total | 5 (0.4%) | 0 (0.0%) | 5 (0.2%) |

**Table S6e. Grade 2 events assessed by the managing clinicians as related to the study product (page 1 of 3)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n | (%) | Dapivirine (N=1313) n | (%) | Total (N=2629) n | (%) |
|---|---|---|---|---|---|---|
| **Participants with Grade 2 or Higher Adverse Experiences Related to Study Product** | | | | | | |
| Related | 9 | (0.7%) | 7 | (0.5%) | 16 | (0.6%) |
| Total | 9 | (0.7%) | 7 | (0.5%) | 16 | (0.6%) |
| **General disorders and administration site conditions** | | | | | | |
| Application site pain | | | | | | |
| Related | 2 | (0.2%) | 0 | (0.0%) | 2 | (0.1%) |
| Total | 2 | (0.2%) | 0 | (0.0%) | 2 | (0.1%) |
| **Infections and infestations** | | | | | | |
| Cervicitis | | | | | | |
| Related | 1 | (0.1%) | 1 | (0.1%) | 2 | (0.1%) |
| Total | 1 | (0.1%) | 1 | (0.1%) | 2 | (0.1%) |
| Pelvic inflammatory disease | | | | | | |
| Related | 1 | (0.1%) | 0 | (0.0%) | 1 | (<.1%) |
| Total | 1 | (0.1%) | 0 | (0.0%) | 1 | (<.1%) |
| Urinary tract infection | | | | | | |
| Related | 1 | (0.1%) | 1 | (0.1%) | 2 | (0.1%) |
| Total | 1 | (0.1%) | 1 | (0.1%) | 2 | (0.1%) |
| **Investigations** | | | | | | |
| Neutrophil count decreased | | | | | | |
| Related | 1 | (0.1%) | 0 | (0.0%) | 1 | (<.1%) |
| Total | 1 | (0.1%) | 0 | (0.0%) | 1 | (<.1%) |
| **Metabolism and nutrition disorders** | | | | | | |
| Abnormal loss of weight | | | | | | |
| Related | 1 | (0.1%) | 0 | (0.0%) | 1 | (<.1%) |
| Total | 1 | (0.1%) | 0 | (0.0%) | 1 | (<.1%) |

**Table S6e. Grade 2 events assessed by the managing clinicians as related to the study product (page 2 of 3)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Nervous system disorders** | | | |
| Headache | | | |
| Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| **Renal and urinary disorders** | | | |
| Urinary incontinence | | | |
| Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| **Reproductive system and breast disorders** | | | |
| Cervix erythema | | | |
| Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Cervix oedema | | | |
| Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Dysmenorrhoea | | | |
| Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Dyspareunia | | | |
| Related | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Total | 0 (0.0%) | 1 (0.1%) | 1 (<.1%) |
| Pelvic pain | | | |
| Related | 1 (0.1%) | 2 (0.2%) | 3 (0.1%) |
| Total | 1 (0.1%) | 2 (0.2%) | 3 (0.1%) |

**Table S6e. Grade 2 events assessed by the managing clinicians as related to the study product (page 3 of 3)**

| MedDRA System Organ Class and Preferred Term/ Maximum Relationship to Study Product | Placebo (N=1316) n (%) | Dapivirine (N=1313) n (%) | Total (N=2629) n (%) |
|---|---|---|---|
| **Reproductive system and breast disorders (continued)** | | | |
| Vulvovaginal pruritus | | | |
| Related | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |
| Total | 1 (0.1%) | 0 (0.0%) | 1 (<.1%) |

| Table S7. Incident sexually transmitted infections during follow-up, by study arm | | |
|---|---|---|
| | **Placebo Vaginal Ring (n=1316)** | **Dapivirine Vaginal Ring (n=1313)** |
| *Chlamydia trachomatis* | | |
| Number of cases during follow-up | 368 | 359 |
| Incidence per 100 person-years (95% CI) | 17.7 (15.9-19.6) | 17.4 (15.7-19.3) |
| *Neisseria gonorrhoeae* | | |
| Number of cases during follow-up | 190 | 170 |
| Incidence per 100 person-years (95% CI) | 9.1 (7.9-10.5) | 8.2 (7.0-9.6) |
| *Trichomonas vaginalis* | | |
| Number of cases during follow-up | 183 | 190 |
| Incidence per 100 person-years (95% CI) | 8.8 (7.6-10.2) | 9.3 (8.0-10.7) |

Testing and treatment for sexually transmitted infections were performed semi-annually and more frequently when clinically indicated.

**Table S8. Proportion of HIV-1 seroconverters with antiretroviral resistance, by randomization arm**

Plasma samples for HIV-1 antiretroviral resistance testing were obtained at the visit at which HIV-1 seroconversion was detected (at which time study medication was withdrawn). Resistance testing was successfully completed on plasma from 170/174 (98%) participants, which included 3/3 participants acutely infected at enrollment, 164/168 HIV-1 seroconverters while on study product, and 3/3 participants who seroconverted after their product use end visit. Overall, 4 participants did not have a resistance result, 3 because of insufficient copies of HIV-1 RNA for extraction (<200 copies/mL) and 1 because of PCR amplification failure.

RNA extracted from plasma was reverse transcribed and HIV-1 *pol* was PCR amplified and sequenced using an in-house Sanger sequencing-based population genotyping assay optimized for non-B HIV-1 subtypes. Population sequences spanned from protease codon 1 through reverse transcriptase codon 335. The testing laboratory (Microbicide Trials Network Virology Core, University of Pittsburgh School of Medicine, Division of Infectious Diseases) was certified to perform the in-house genotyping assay by CLIA and the NIH-sponsored Viral Quality Assurance (VQA) Program at Rush Presbyterian, Chicago, IL. Mutations in HIV-1 Group M subtype were identified using the Stanford HIV-1 Drug Resistance Database version 7.0.

The frequency of all non-nucleoside reverse transcriptase (NNRTI) mutations were evaluated as mutations of potential clinical significance for resistance to dapivirine. Of the 164 participants with successful viral resistance results within the intention-to-treat cohort (i.e., excluding acutely infected participants and participants that seroconverted after cessation of product use), 10 out of 96 (10.4%) in the placebo arm had any NNRTI resistant strain, and 8 out of 68 (11.8%) in the dapivirine arm had any NNRTI resistant strain. The overall occurrence of NNRTI mutations was not different by arm (Fisher's Exact Test: 0.19, p=0.80).

Additional analyses examined the frequencies of a subset of four NNRTI resistance mutations including L100I, K103N, E138K and Y181C because of their potential relationship to dapivirine resistance based on *in vitro* selection studies.[10] No subjects had HIV-1 with the E138K, L100I or Y181C detected. Four subjects had HIV-1 with the K103N mutation however the frequency of K103N detection did not differ by arm (Table S6A). Other NNRTI mutations detected included V90I, K101E, K103S, V106M,

V108I, E138A/G, V179D/I/T and H221Y but the frequency of detection of these mutations also did not differ by arm (Table S6B). Several NNRTI mutations were observed to occur in combination, including E138A or G with V179D/I/T (n=2), V108I (n=1) or K101E (n=2); K103S with V106M (n=1) and V90I with K103N (n=2), but the frequency of more than one NNRTI mutation was not different between study arms.

| Table S8A. Non-nucleoside reverse transcriptase mutation conferring potential resistance to dapivirine | | |
|---|---|---|
| | **Placebo Vaginal Ring** | **Dapivirine Vaginal Ring** |
| **L100I** | | |
| Overall | 0/101 (0%) | 0/69 (0%) |
| Among subjects retrospectively found to be HIV-1 infected at enrollment | 0/3 (0%) | 0/0 (0%) |
| Among subjects who acquired HIV-1 infection after enrollment while on study product | 0/96 (0%) | 0/68 (0%) |
| Among subjects who acquired HIV-1 infection after the product use end visit | 0/2 (0%) | 0/1 (0%) |
| **K103N** | | |
| Overall | 2/101 (2.0%) | 2/69 (2.9%) |
| Among subjects retrospectively found to be HIV-1 infected at enrollment | 0/3 (0%) | 0/0 (0%) |
| Among subjects who acquired HIV-1 infection after enrollment | 1/96 (1.0%) | 2/68 (2.9%) |
| Among subjects who acquired HIV-1 infection after the product use end visit | 1/2 (50.0%) | 0/1 (0%) |
| **E138K** | | |
| Overall | 0/101 (0%) | 0/69 (0%) |
| Among subjects retrospectively found to be HIV-1 infected at enrollment | 0/3 (0%) | 0/0 (0%) |
| Among subjects who acquired HIV-1 infection after enrollment | 0/96 (0%) | 0/68 (0%) |
| Among subjects who acquired HIV-1 infection after the product use end visit | 0/2 (0%) | 0/1 (0%) |
| **Y181C** | | |
| Overall | 0/101 (0%) | 0/69 (0%) |
| Among subjects retrospectively found to be HIV-1 infected at enrollment | 0/3 (0%) | 0/0 (0%) |
| Among subjects who acquired HIV-1 infection after enrollment | 0/96 (0%) | 0/68 (0%) |
| Among subjects who acquired HIV-1 infection after the product use end visit | 0/2 (0%) | 0/1 (0%) |

| Table S8B. Non-nucleoside reverse transcriptase mutations of potential clinical significance among subjects who acquired HIV-1 after enrollment* | | |
|---|---|---|
| | **Placebo Vaginal Ring** | **Dapivirine Vaginal Ring** |
| V90I | 1/96 (1.0%) | 2/68 (2.9%) |
| K101E | 1/96 (1.0%) | 1/68 (1.5%) |
| K103S | 0/96 (0%) | 1/68 (1.5%) |
| V106M | 0/96 (0%) | 1/68 (1.5%) |
| V108I | 0/96 (0%) | 1/68 (1.5%) |
| E138A | 5/96 (5.2%) | 3/68 (4.4%) |
| E138G | 0/96 (0%) | 1/68 (1.5%) |
| V179D | 2/96 (2.1%) | 1/68 (1.5%) |
| V179I/T | 0/96 (0%) | 1/68 (1.5%) |
| H221Y | 1/96 (1.0%) | 1/68 (1.5%) |

* No instances of these mutations occurred in subjects retrospectively found to be HIV-1 infected at enrollment or among subjects who acquired HIV-1 infection after the product use end visit.

**Supplementary Figure Legends.**

**Figure S1.** **HIV-1 testing algorithm.** All study sites performed HIV-1 testing using a standard algorithm. All sites were validated in the algorithm prior to initiating the study and all participated in ongoing proficiency testing throughout the course of the study. The HIV-1 test kits used at each site were pre-approved prior to use; at each testing time point when rapid tests were used at least one FDA-approved rapid test kit was used. If rapid HIV-1 testing found a positive result for either or both rapid assays, confirmatory HIV-1 Western blot and RNA PCR were done, as well as testing for antiretroviral resistance. All Western blot testing was performed using FDA-approved test kits. Individuals acquiring HIV-1 were offered to continue with follow-up and were referred to local services for HIV-1 care and support. Seroconversion events were adjudicated by an HIV-1 endpoints committee that was blinded to randomization assignment.

**Figure S2.** **Dapivirine detection in plasma during follow-up, a) overall and b) by study site.** Plasma was collected at quarterly follow-up visits and was tested for all available samples (n=9,459) for participants assigned to the trial's active dapivirine ring arm. In phase I/II studies, plasma concentrations >95 pg/mL were achieved in most subjects within 8 hours of ring use and thus concentrations >95 pg/mL were interpreted as indicating adherence to the dapivirine ring (dark purple). Concentrations between the lower limit of quantification (LLQ, 20 pg/mL) and 95 pg/mL potentially reflected adherence or, alternatively, use of the ring for only a few hours prior to the scheduled clinic visit (i.e., "white coat dosing") (medium purple). Levels below the LLQ (BLQ) reflected non-use of the ring (light purple). Visits at which the participant was on a protocol-defined product hold (e.g., due to pregnancy) or at which a sample was not available are also indicated (dark green and light green, respectively). The frequency of detection of dapivirine at concentrations >95 pg/mL increased over follow-up (generalized linear mixed model with random intercepts and adjusted for country, $p<0.001$). The >95 pg/mL cut-off was chosen to distinguish cases in which the ring was removed during the month and then reinserted immediately prior to a clinic visit (i.e., <8 hours). In a prior study of this ring, when the ring was placed under observation, it required at least 8 hours for plasma dapivirine concentrations to exceed 95 pg/mL in nearly all (88%) research participants.[11,12] In that same study, plasma dapivirine concentrations exceeded this concentration in nearly all (88%) participants for at least 24 hours after removal of the ring per protocol after 28 days. Thus, the use of the >95 pg/mL cut-off to define adherence may overestimate adherence for women who removed the vaginal ring for most of the month but reinserted >8 hours prior to a clinic visit.

**Figure S3.** **Dapivirine detection in returned, used rings: a) boxplot of dapivirine in returned rings by concentration of dapivirine in concurrently collected plasma and b) distribution of dapivirine quantity in returned rings and in unused control rings.**

Dapivirine was quantified in returned, used rings for subjects assigned to the active dapivirine vaginal ring arm. In total, 20,770 rings were tested, and for 7,106 visits, concurrently collected plasma was available (plasma was collected quarterly while rings were collected monthly). Dapivirine rings were loaded with 25 mg of dapivirine and, in phase I/II studies, released ~4 mg of dapivirine over a month of continuous use. In returned, used rings residual levels less than 23.5 mg were defined as adherent, to take into account dapivirine release across different individuals and allowed assay performance.

For Figure S3a, results are presented by plasma concentrations: below the lower limit of quantification (LLQ = 20 pg/mL) (BLQ), LLQ to 95 pg/mL, and >95 pg/mL. Adjusting for

site and visit, compared to rings from women with no detectable plasma dapivirine (BLQ), the average amount of dapivirine remaining in a ring was 0.29 mg (95% CI 0.07-0.51, p=0.01) less in women with plasma levels between LLQ and 95pg/mL and 2.6 mg (95% CI 2.37-2.77, p<0.001) less in plasma levels above 95 pg/mL.

Figure S3b shows the probability distribution functions for the amount of dapivirine measured in rings returned at visits where a participant's plasma dapivirine level was greater than 95 pg/mL (green) or less than 95 pg/mL (red). In addition, the probability distribution for unused active dapivirine arm rings, which were tested with each batch as an internal control, is presented (black). The grey line segment indicates a residual dapivirine amount of 23.5 mg, the definition proposed prior to the conclusion of the study that would define adherence. For control rings (which had not been used), 2.5% had dapivirine levels measured at less than 23.5 mg. The graph illustrates that, in general, visits at which plasma dapivirine concentrations were less than 95 pg/mL had residual dapivirine amounts in the rings relatively similar to, although lower than, control rings, while visits at which plasma dapivirine concentrations were greater than 95 pg/mL had lower residual dapivirine amounts. However, there was overlap in the distributions.

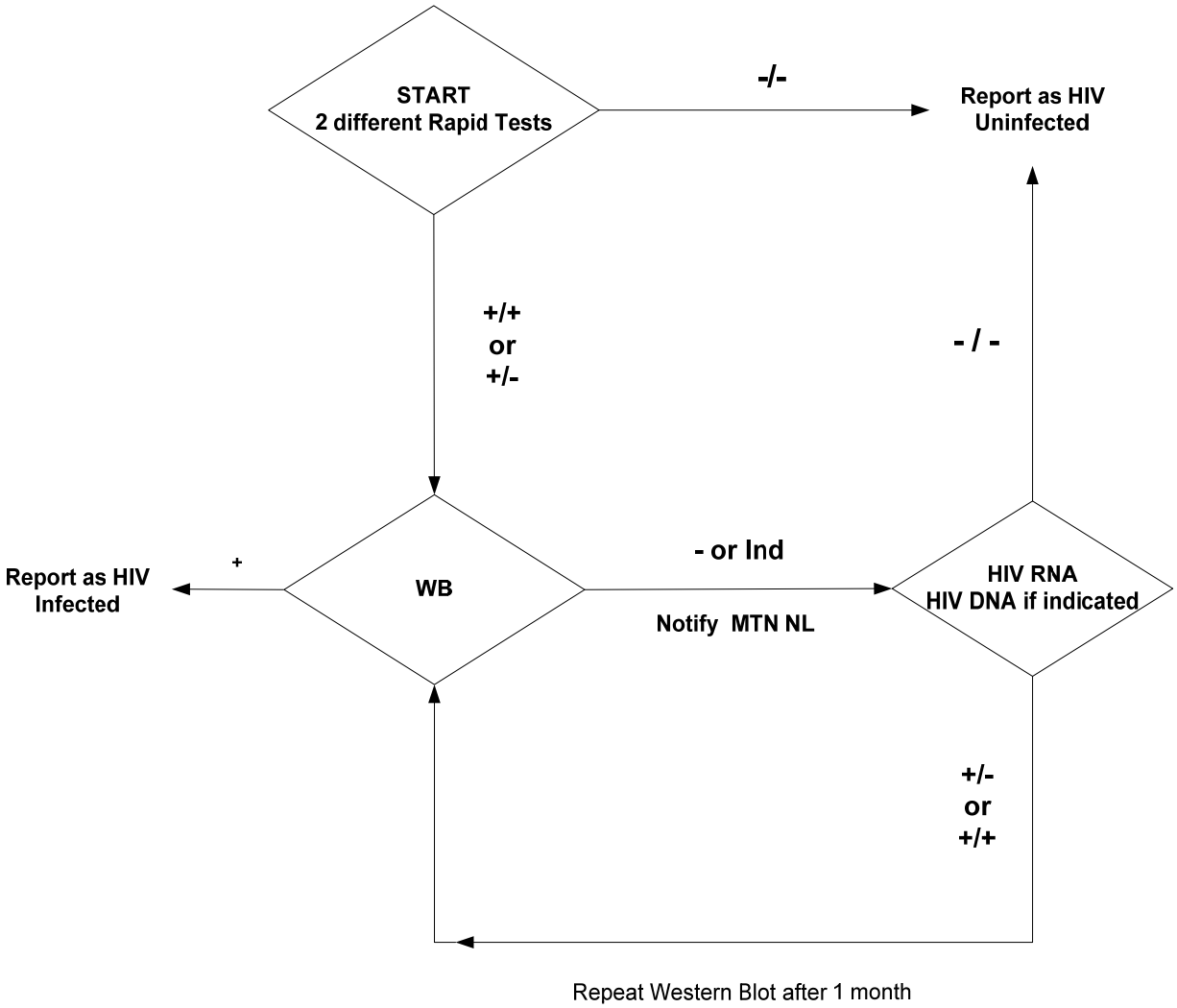
Thus, both the plasma dapivirine concentration of >95 pg/mL and the residual ring amount of <23.5 mg are susceptible to defining a visit as adherent when adherence was not necessarily sustained for the prior month.

**Figure S4.** **HIV-1 incidence by study arm, overall and among pre-specified subgroups.** Overall analyses include data from all 15 sites and from 13 of the 15 sites (i.e., excluding data from two sites, observed early in the study to have lower retention and adherence compared to other sites). The two excluded sites were among nine sites located in South Africa, seven of which were located in the KwaZulu-Natal province. Excluding those two sites, the relative risk reduction for HIV-1 for South Africa sites was 38% (95% CI 7-58%, p=0.02, n=100 events) and for KwaZulu-Natal 36% (95% CI 0-600%, p=0.05, n=78 events). The p-values for overall intention-to-treat analyses apply to the hypothesis of any evidence of HIV-1 protection (i.e., testing against a null hypothesis of 0%), which was defined in the trial's Statistical Analysis Plan as the primary trial comparison.

Pre-specified subgroup analyses – defined by age, country, educational status, marital status, the presence of a sexually transmitted infection at baseline, number of sexual partners, and whether women reported informing their primary partner about their use of the vaginal ring – were planned. For the subgroup analyses, p-values correspond to a test for significant interaction in the site-stratified Cox proportional hazards model. In the forest plots, dashed line indicates HR of 1.0 (0% HIV-1 protection). Subgroup analyses exclude information from two study sites defined early in the study period as having lower than anticipated retention and adherence.

**Figure S5.** **Adverse events occurring in >0.5% of the study population.** Adverse events are ordered by the magnitude of difference between the study arms (dapivirine minus placebo). Blue triangles and red circles indicate the absolute proportion of subjects experiencing each adverse event in the dapivirine and placebo arms, respectively. Forest plots define the difference in frequency and 95% confidence interval. The study database recorded all Grade 2 or higher adverse events as well as all Grade 1 laboratory and genitourinary system events, regardless of assessed relationship to the study product.

**Figure S1. HIV-1 testing algorithm**




Ind: Indeterminate test results

**Figure S2a. Dapivirine detection in plasma during follow-up**

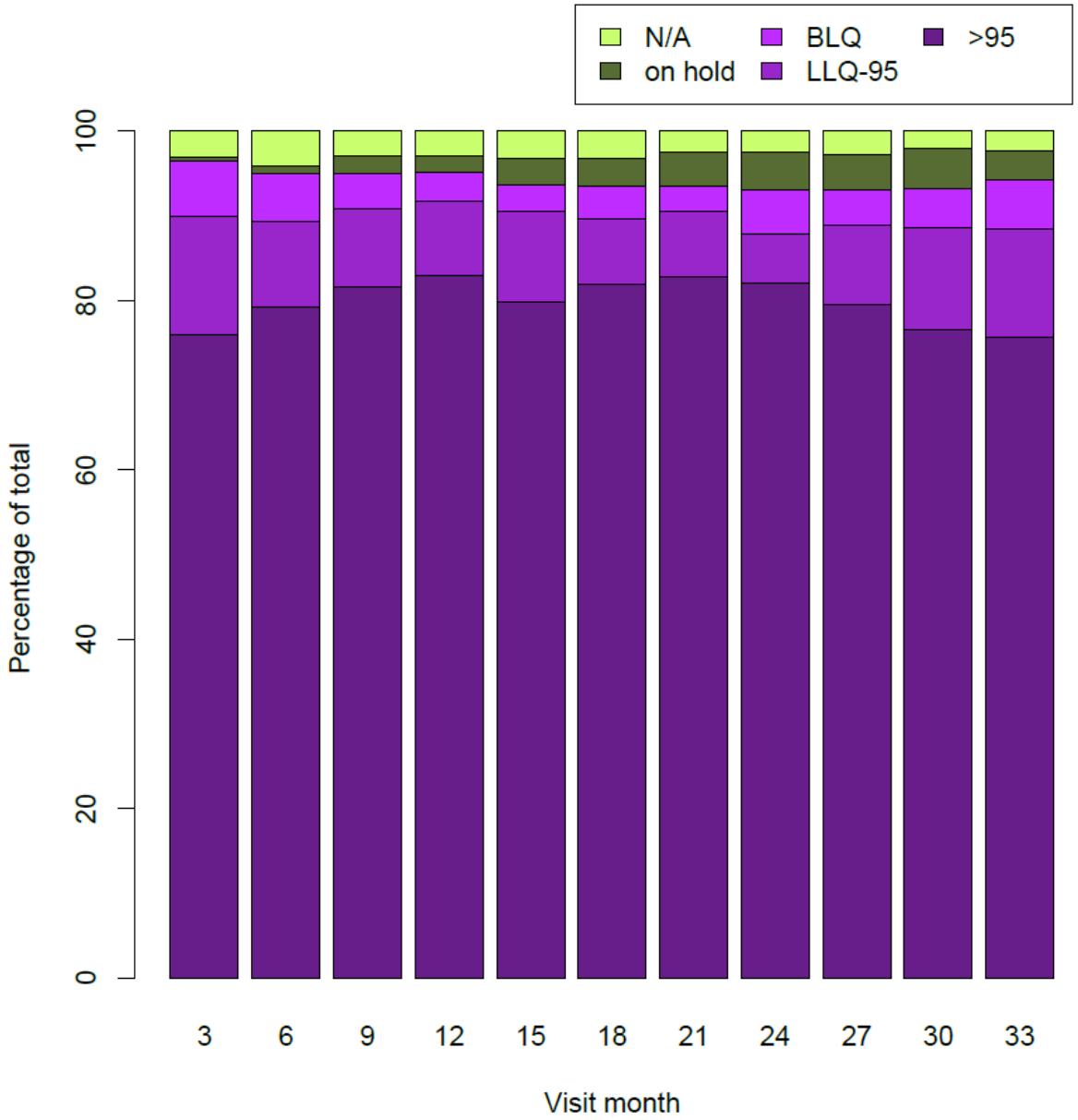


**Figure S2b. Dapivirine detection in plasma during follow-up, by study site**

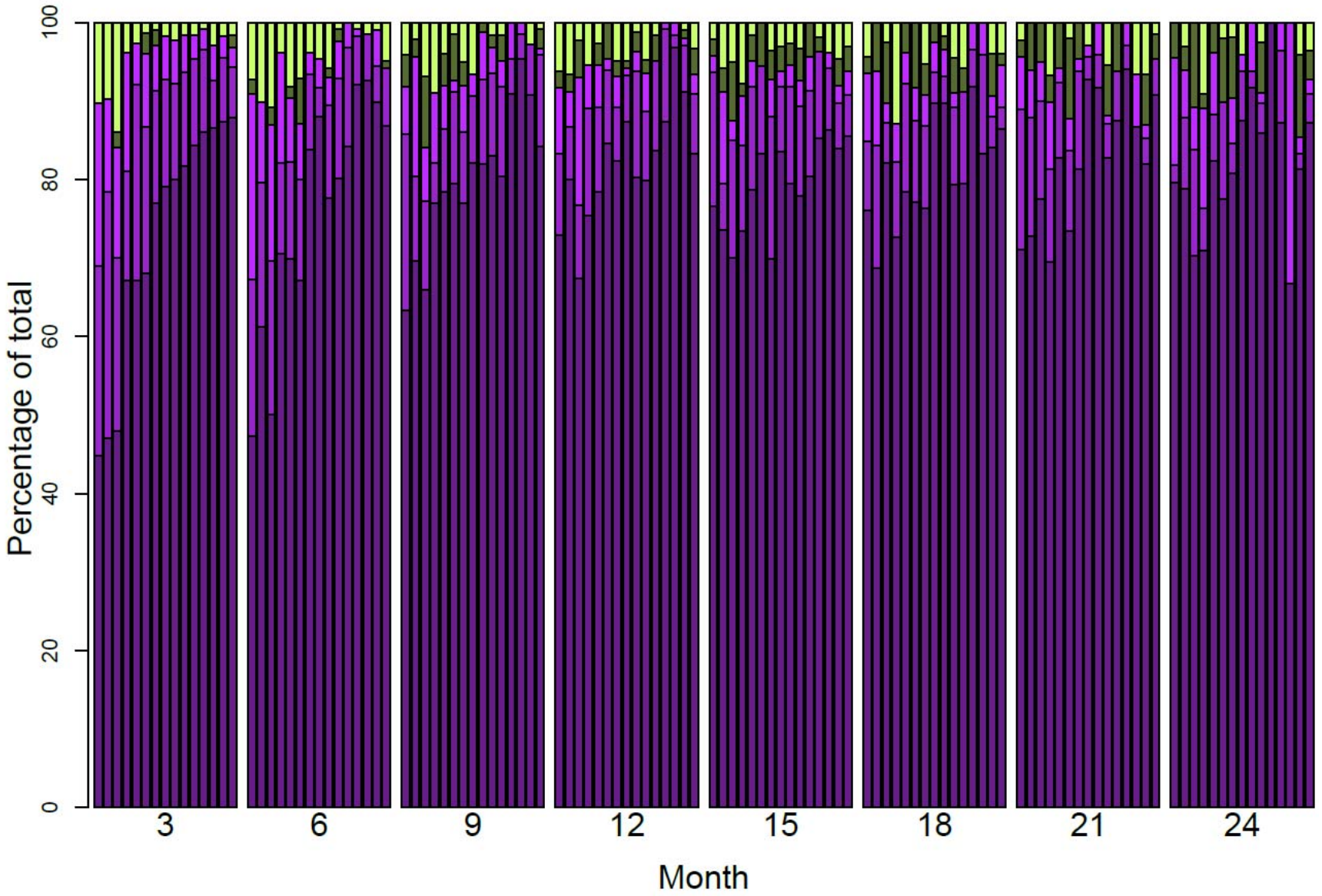


**Figure S3a. Dapivirine detection in returned, used rings, by concentration of dapivirine in concurrently collected plasma**

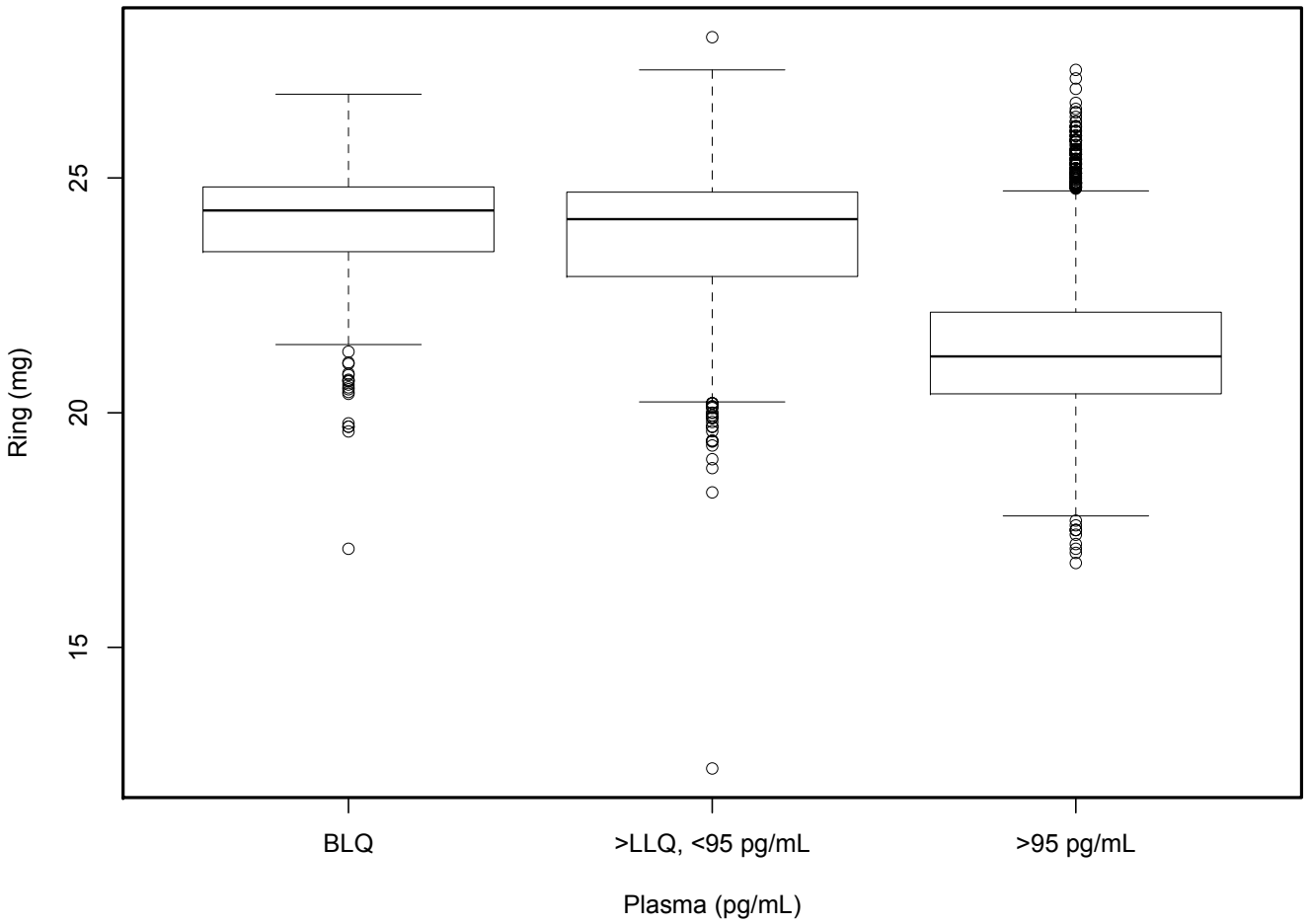


**Figure S3b. Distribution of dapivirine quantity in returned rings and in unused control rings**

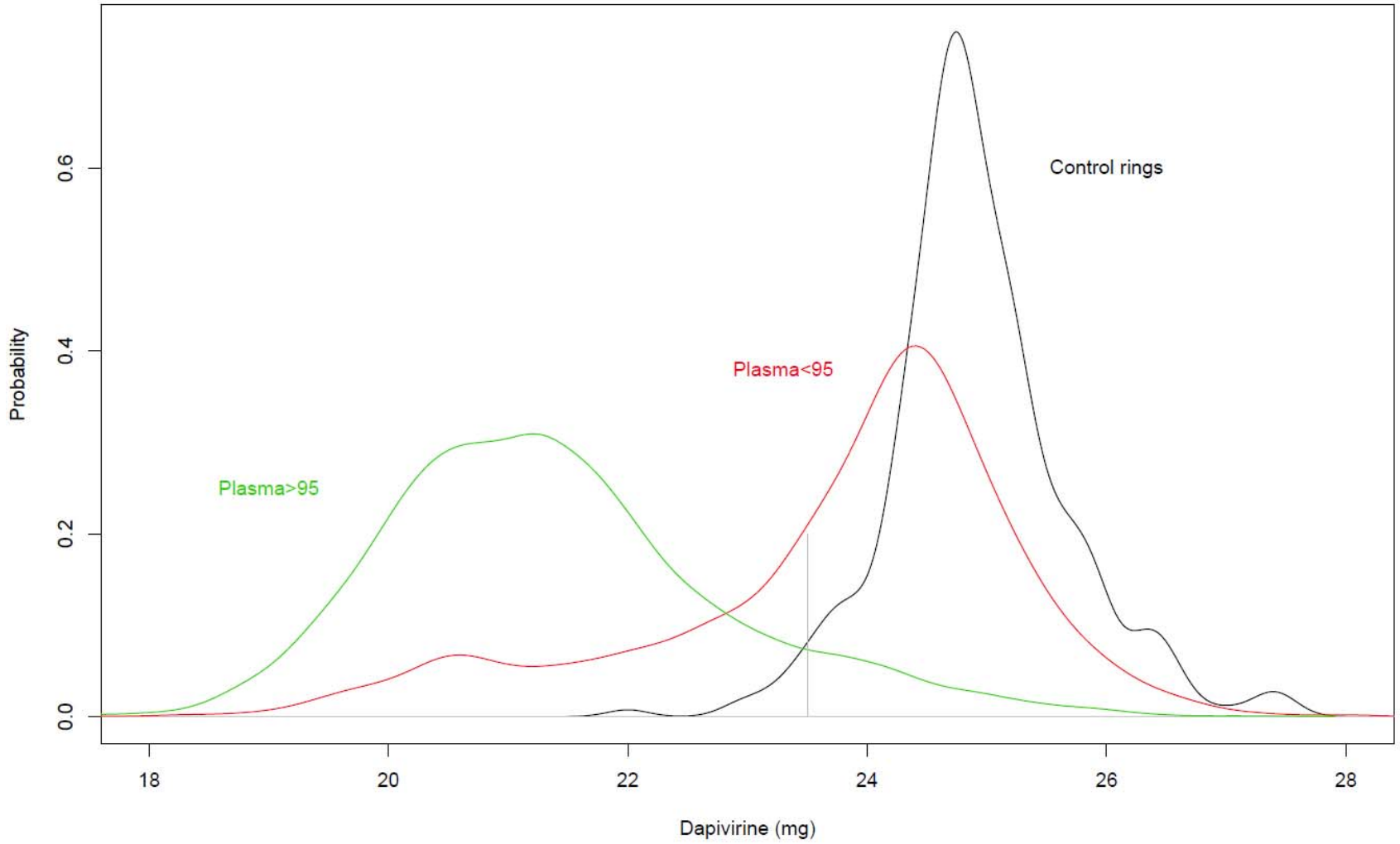


**Figure S4. HIV-1 incidence by study arm, overall and among pre-defined subgroups.**

| Subgroup | Placebo | Dapivirine | Hazard Ratio (95% CI) Dapivirine vs. Placebo | P Value |
|---|---|---|---|---|
| | *no. of events/total no. (rate per 100 person-yr)* | | | |
| 15 Sites | 97/1313 (4.54) | 71/1313 (3.31) | 0.73 (0.54-0.99) | 0.05 |
| 13 Sites | 85/1203 (4.44) | 54/1203 (2.78) | 0.63 (0.44-0.88) | 0.01 |
| Age of participant | | | | 0.02 |
| <25 yr | 40/452 (5.70) | 36/446 (5.05) | 0.90 (0.57-1.41) | |
| >= 25 yr | 45/751 (3.71) | 18/756 (1.47) | 0.39 (0.23-0.68) | |
| Country | | | | 0.98 |
| South Africa | 61/601 (6.17) | 39/603 (3.84) | 0.62 (0.42-0.93) | |
| Malawi, Uganda, and Zimbabwe | 24/602 (2.59) | 15/600 (1.62) | 0.63 (0.33-1.20) | |
| Educational status | | | | 0.49 |
| No secondary school | 14/187 (4.74) | 7/205 (2.18) | 0.46 (0.19-1.15) | |
| Some secondary school or higher | 71/1016 (4.38) | 47/998 (2.90) | 0.66 (0.45-0.95) | |
| Marital status | | | | 0.67 |
| Non-married | 67/661 (6.32) | 45/681 (4.00) | 0.64 (0.44-0.93) | |
| Married | 18/541 (2.10) | 9/522 (1.10) | 0.53 (0.24-1.17) | |
| STIs at baseline | | | | 0.30 |
| No | 56/962 (3.65) | 30/952 (1.93) | 0.53 (0.34-0.83) | |
| Yes | 29/241 (7.63) | 24/251 (6.20) | 0.78 (0.45-1.34) | |
| Number of sexual partners | | | | 0.96 |
| 0-1 | 64/991 (4.11) | 41/1008 (2.58) | 0.63 (0.42-0.93) | |
| 2+ | 21/211 (5.86) | 13/195 (3.70) | 0.62 (0.31-1.23) | |
| Partner knowledge of ring use | | | | 0.50 |
| Does not know | 34/415 (4.98) | 26/426 (3.64) | 0.71 (0.43-1.19) | |
| Knows | 51/788 (4.13) | 28/777 (2.28) | 0.56 (0.35-0.89) | |

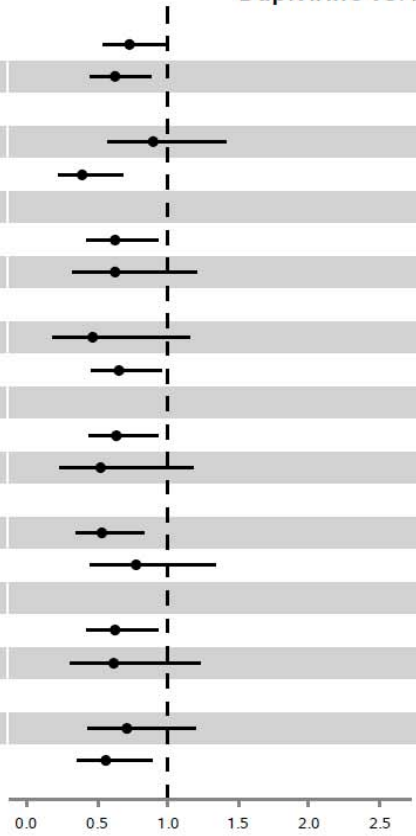
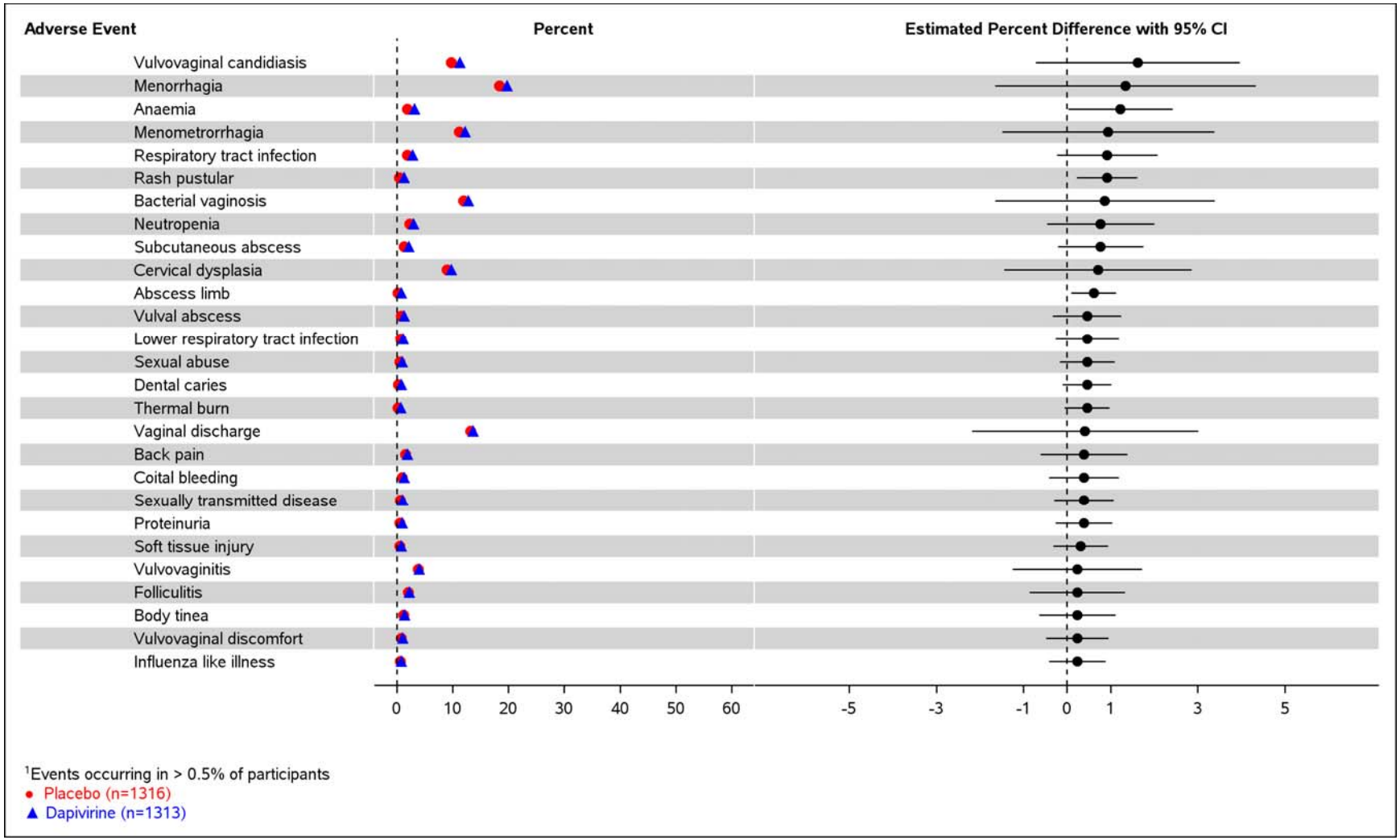
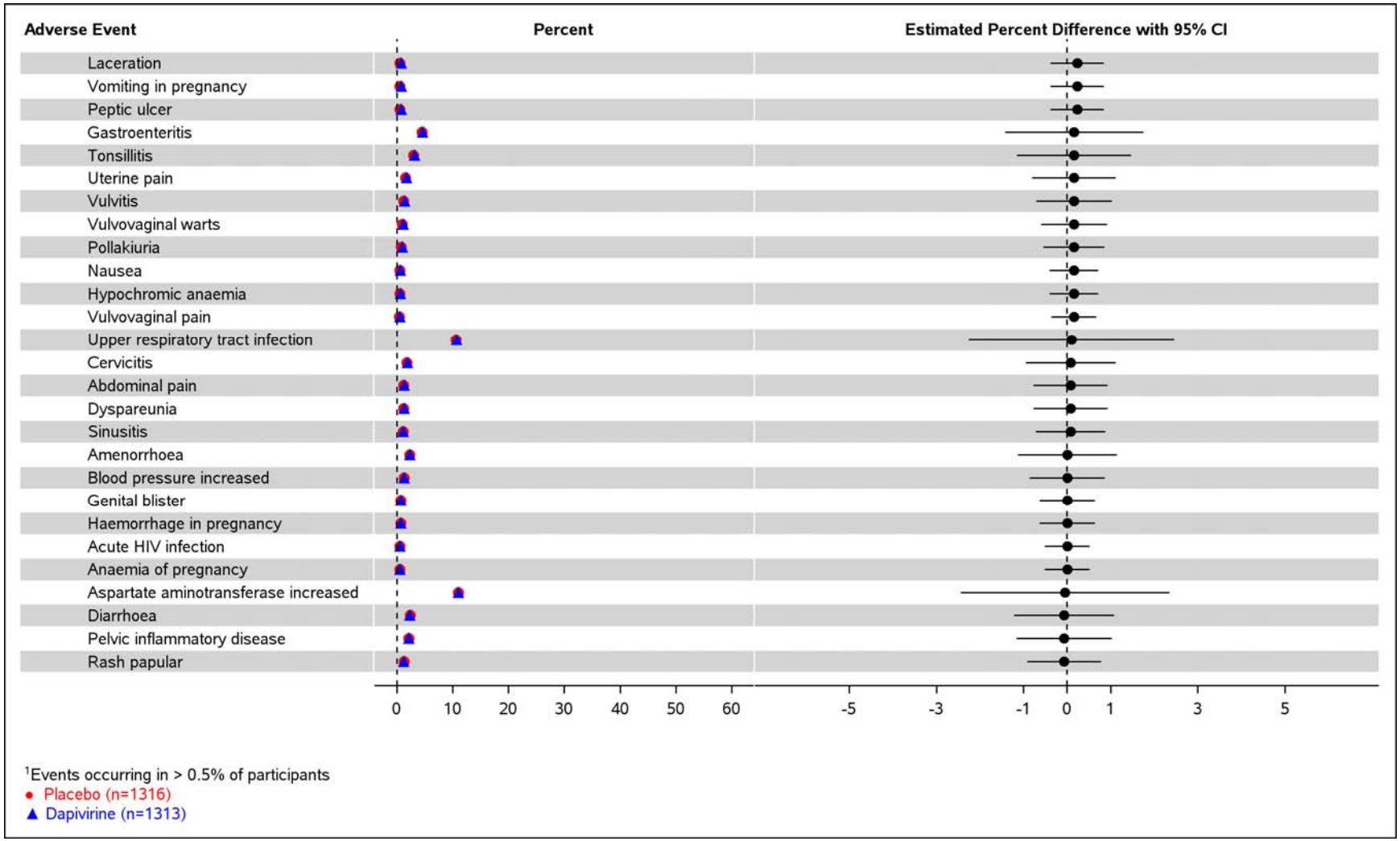
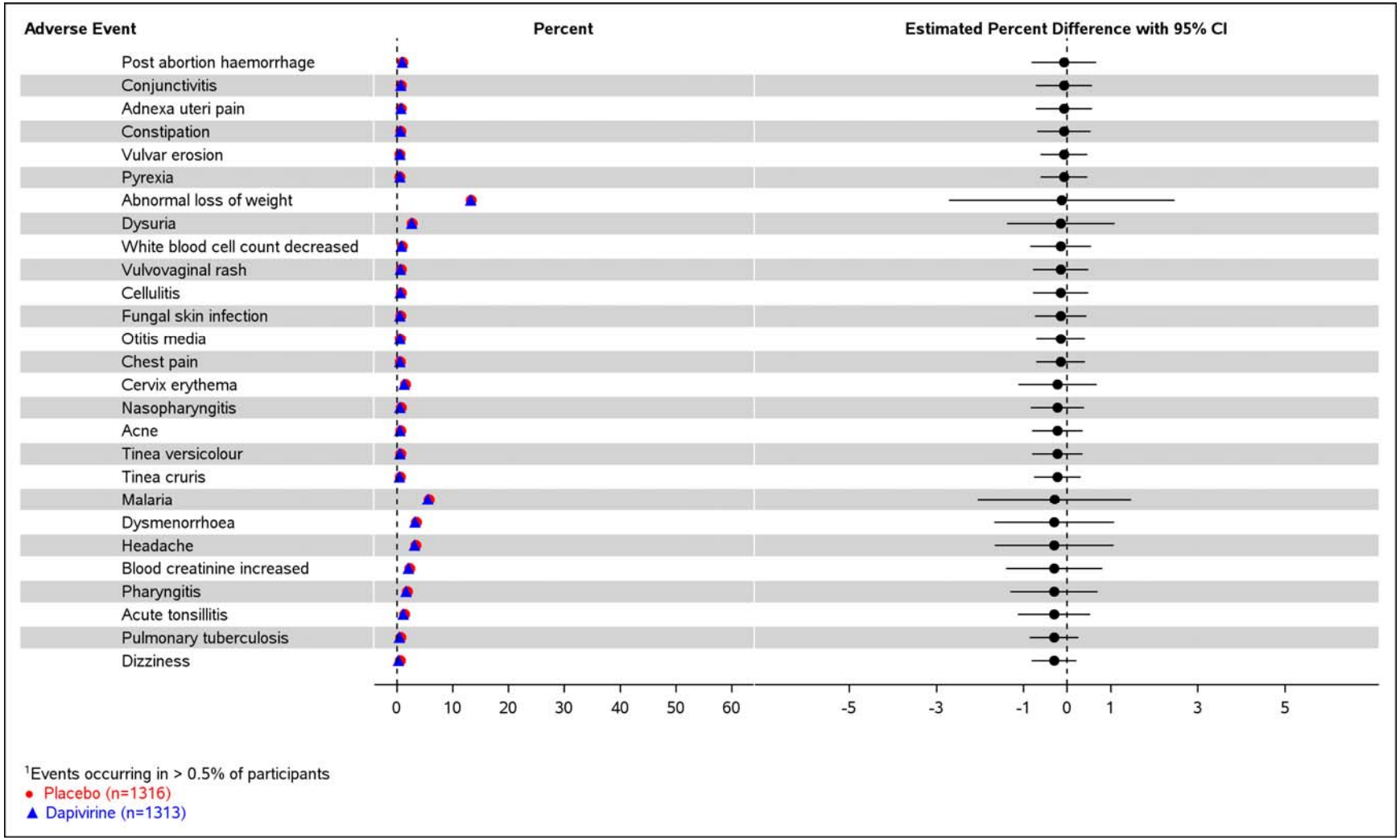


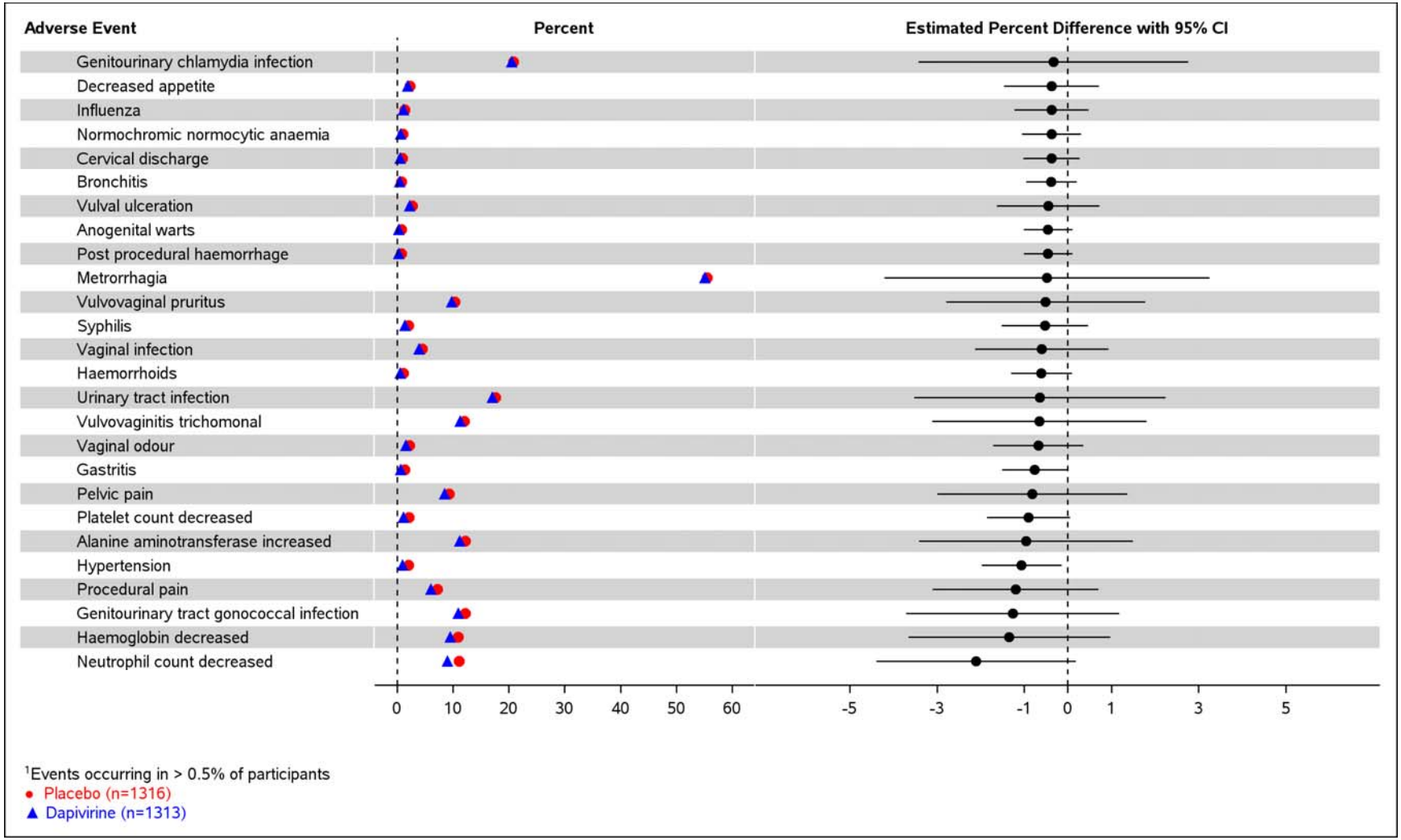
**Figure S5. Adverse events occurring in >0.5% of the study population (in addition to Table 2) [4 pages]**






[1]Events occurring in > 0.5% of participants
● Placebo (n=1316)
▲ Dapivirine (n=1313)


Adverse Event
Percent
Estimated Percent Difference with 95% CI
Post abortion haemorrhage
Conjunctivitis
Adnexa uteri pain
Constipation
Vulvar erosion
Pyrexia
Abnormal loss of weight
Dysuria
White blood cell count decreased
Vulvovaginal rash
Cellulitis
Fungal skin infection
Otitis media
Chest pain
Cervix erythema
Nasopharyngitis
Acne
Tinea versicolour
Tinea cruris
Malaria
Dysmenorrhoea
Headache
Blood creatinine increased
Pharyngitis
Acute tonsillitis
Pulmonary tuberculosis
Dizziness
0
10
20
30
40
50
60
-5
-3
-1
0
1
3
5
[1]Events occurring in > 0.5% of participants
Placebo (n=1316)
Dapivirine (n=1313)


Adverse Event
Percent
Estimated Percent Difference with 95% CI
Genitourinary chlamydia infection
Decreased appetite
Influenza
Normochromic normocytic anaemia
Cervical discharge
Bronchitis
Vulval ulceration
Anogenital warts
Post procedural haemorrhage
Metrorrhagia
Vulvovaginal pruritus
Syphilis
Vaginal infection
Haemorrhoids
Urinary tract infection
Vulvovaginitis trichomonal
Vaginal odour
Gastritis
Pelvic pain
Platelet count decreased
Alanine aminotransferase increased
Hypertension
Procedural pain
Genitourinary tract gonococcal infection
Haemoglobin decreased
Neutrophil count decreased
0 10 20 30 40 50 60
-5 -3 -1 0 1 3 5
[1]Events occurring in > 0.5% of participants
Placebo (n=1316)
Dapivirine (n=1313)

**Supplementary Materials References**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