

World Leaders Recommit to Ending Neglected Tropical Diseases, Citing Remarkable Progress Since 2012

Governments and private donors pledge US\$812 million around five-day summit in Geneva; World Health Organization releases data showing medicines to prevent NTDs reach nearly a billion people each year

GENEVA (19 April 2017) – This week, leaders from governments, pharmaceutical companies and charitable organizations convened at a five-day summit in Geneva to pledge new commitments to the collective efforts to control and eliminate neglected tropical diseases (NTDs). The summit coincided with the launch of the World Health Organization’s (WHO) Fourth Report on NTDs, showing transformational progress against these debilitating diseases, and a commitment by the United Kingdom to more than double its funding for NTDs.

The meeting comes five years after the launch of the [London Declaration on NTDs](#), a commitment by the public and private sectors to achieve the WHO goals for control, elimination and eradication of 10 NTDs. In that time, billions of treatments have been donated by pharmaceutical companies and delivered to impoverished communities in nearly 150 countries, reaching nearly a billion people in 2015.

NTDs are some of the oldest and most painful diseases, afflicting the world’s poorest communities. One in six people suffer from NTDs worldwide, including more than half a billion children. NTDs disable, debilitate and perpetuate cycles of poverty, keeping children out of school, parents out of work, and dampening hope of any chance of an economic future.

New Report Shows Dramatic Progress

A new report titled [Integrating Neglected Tropical Diseases in Global Health and Development](#) by the WHO revealed that more people are being reached with needed NTD interventions than ever before. In 2015, nearly a billion people received treatments donated by pharmaceutical companies for at least one NTD, representing a 36 percent increase since 2011, the year before the launch of the London Declaration. As more districts, countries and regions eliminate NTDs, the number of people requiring treatments has decreased from 2 billion in 2010 to 1.6 billion in 2015.

“WHO has observed record-breaking progress towards bringing ancient scourges like sleeping sickness and elephantiasis to their knees,” says WHO Director-General, Dr. Margaret Chan. “Over the past 10 years, millions of people have been rescued from disability and poverty, thanks to one of the most effective global partnerships in modern public health.”

The report detailed progress against each disease, citing countries and regions that are reaching control and elimination goals for specific NTDs. Highlights include:

- **Lymphatic filariasis (LF) racing toward finish line:** In the last year, eight countries (Cambodia, Cook Islands, Maldives, Marshall Islands, Niue, Sri Lanka, Togo and Vanuatu) eliminated LF, and 10 other countries are waiting on surveillance results to verify elimination. Thanks to strong programs, the number of people globally requiring preventative treatment has dropped from 1.4 billion in 2011 to fewer than 950 million in 2015.
- **Fewest-ever cases of human African trypanosomiasis (HAT, or sleeping sickness):** In 2015, there were fewer reported cases of sleeping sickness than any other year in history, with fewer than 3,000 cases worldwide – an 89 percent reduction since 2000. Innovative vector control and diagnostic technologies, supported by increasing numbers of product development partnerships, are revolutionizing sleeping sickness diagnosis, prevention and treatment.
- **Eighty-two percent decrease in visceral leishmaniasis (VL) cases in India, Nepal and Bangladesh:** Since 2008, cases of VL across India, Nepal and Bangladesh have decreased by 82 percent due to improvements in vector control, social mobilization of village volunteers, collaboration with other NTD programs and drug

donations from industry partners.

- **Guinea worm disease nearing eradication:** Cases of Guinea worm disease have reduced from an estimated 3.5 million in 1986 to just 25 human cases in 2016 in just three countries – Chad, Ethiopia and South Sudan.

Global Donors Pledge Additional Support

Governments and other donors announced new commitments at the summit to expand the reach and impact of NTD programs around the world. The Bill & Melinda Gates Foundation committed \$335 million in grants over the next four years to support a diverse group of NTD programs focused on drug development and delivery, disease surveillance and vector control. The commitment includes \$42 million to support The Carter Center’s guinea worm eradication initiative, as well as dedicated funding to accelerate the elimination of African sleeping sickness.

“NTDs are some of the most painful, debilitating and stigmatizing diseases that affect the world’s poorest communities. That’s why we helped launch the London Declaration, a historic milestone that led to significant progress in treating and reducing the spread of NTDs and demonstrated the impact that the public sector, the private sector, communities and NGOs can have by working together,” said Bill Gates, co-chair of the Bill & Melinda Gates Foundation.

“Thanks to this partnership, these neglected diseases are now getting the attention they deserve so fewer people have to suffer from these treatable conditions. There have been many successes in the past five years, but the job is not done yet. We have set ambitious targets for 2020 that require the continued commitment of pharmaceutical companies, donor and recipient governments, and frontline health workers to ensure drugs are available and delivered to the hardest to reach people.”

The Belgian government also pledged an additional \$27 million, spread equally over the next nine years, toward the elimination of sleeping sickness in the Democratic Republic of the Congo (DRC). This amount will be matched for the next three years by the Bill & Melinda Gates Foundation, establishing a platform for increased collaboration between Belgium, the DRC and the broader NTD partnership.

As part of its commitment to eliminating HAT, Vestergaard pledged to donate 20 percent of its insecticide-treated “tiny targets” used to control the tsetse flies that carry the disease, scaling over the next three years towards 100 percent as elimination nears.

These commitments build on the UK Government’s announcement earlier this week, in which it pledged almost \$450 million over 5 years to support NTD control and elimination efforts around the world.

Industry Contributions Expand Scale and Reach of NTD Program

Progress against NTDs has been enabled by the large-scale donation of medicines by 10 pharmaceutical companies. In the five years since the London Declaration, companies have donated over 7 billion treatments that, with the support of partners, now reach nearly 1 billion people every year. These donations, worth an estimated \$19 billion from 2012 through 2020, greatly multiply the impact of donor investments; USAID estimates that each dollar invested in delivery leverages \$26 worth of donated drugs.

In a [statement](#) released today, industry leaders reaffirmed their 2012 pledge to do their part to beat these diseases, and encouraged other sectors to maintain their commitments as well.

“The London Declaration is a powerful example of the impact of successful partnerships,” said Haruo Naito, CEO of Eisai and an original signatory of the London Declaration. “By leveraging our resources and focusing on a common goal, we are already making unprecedented progress towards eliminating these horrific diseases. The work we are doing today is a long-term investment into a healthier and more prosperous future.”

In addition to donations, pharmaceutical companies are working together and with research institutes to discover and develop new tools to prevent, diagnose and treat NTDs. A [report](#) released today by the International Federation of Pharmaceutical Manufacturers and Associations collected the full scope of industry investment in NTD R&D, including:

- Sanofi and the Drugs for Neglected Diseases *initiative* (DNDi) are developing a new oral drug candidate for HAT, fexinidazole, which would replace the current mixed oral-intravenous drug regimen. Fexinidazole could represent a therapeutic breakthrough which will support sustainable elimination efforts as per the WHO roadmap for 2020. The drug is expected to be submitted for regulatory approval later in 2017.
- Several companies are working to develop pediatric formulations of existing NTD medicines, including Bayer (nifurtimox, for Chagas disease), Merck KGaA (praziquantel, for schistosomiasis), and Elea/Mundo Sano (who are working with DNDi to develop a second pediatric source of benznidazole, for Chagas disease), while Johnson & Johnson (mebendazole, for soil-transmitted helminths) developed a new chewable form of mebendazole, recently approved by the FDA, for children too young to swallow.
- AbbVie, Bayer, Eisai, Johnson & Johnson and Merck KGaA are part of the Macrofilaricide Drug Accelerator Program, an initiative aimed at identifying and generating new drug compounds that can kill the adult worms that cause onchocerciasis and lymphatic filariasis.
- Bayer is working with DNDi to develop emodepside, an oral treatment for lymphatic filariasis and river blindness
- Eisai is working with DNDi to develop ravuconazole, a new oral drug currently in clinical trials for Chagas disease, and is partnering with DNDi to develop ravuconazole in a new disease area, mycetoma.
- GlaxoSmithKline and DNDi have agreed to jointly pursue the pre-clinical development of the two novel candidates for the treatment of visceral leishmaniasis; the candidates were developed by a collaboration between GSK and the University of Dundee's Drug Discovery Unit, and the work was funded by Wellcome. The agreement for pre-clinical development will be conditional on signing an additional agreement.
- In 2015, Eisai, Shionogi, Takeda, AstraZeneca and DNDi launched the [NTD Drug Discovery Booster](#), a multi-company effort to accelerate the discovery of new drugs for leishmaniasis and Chagas disease. In 2016 they were joined by Celgene Global Health. Merck KGaA announced today that it will join the consortium.
- Many companies – including AbbVie, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Chemo, Daiichi Sankyo, Eisai, Elea, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck KGaA, MSD, Novartis, Pfizer, Sanofi, Shionogi, and Takeda – have given DNDi and other non-profits access to their compound libraries and/or contribute scientific and technical expertise to DNDi and conduct pre-clinical and clinical studies to facilitate the development of new drugs to combat various NTDs.
- Gilead is collaborating with the US Department of Defense, Centers for Disease Control and Prevention, and National Institutes of Health as well as multiple academic institutions to discover and develop novel antivirals for highly pathogenic infections and neglected/emerging viral diseases, including dengue fever. GS-5734, Gilead's most advanced investigational agent, is currently being studied in Ebola survivors.

Companies are also working with partners to solve supply chain problems, develop program strategies and build in-country capacity to ensure that drugs, tools and other interventions reach those who need them most.

Addressing the Challenges Ahead

Though tremendous progress has been made in reducing the burden of NTDs, global control and elimination targets cannot be met without increased financial support, stronger political commitment and better tools to prevent, diagnose and treat the diseases. This week, partners from private philanthropy, affected country governments and cross-sector partnerships recommitted to leveraging their respective resources and expertise to fill critical gaps.

Financial Resources

Although nearly a billion people received NTD treatments in 2015, more funding is needed to ensure that NTD programs reach all people and communities affected by the diseases. WHO estimates that 340 million people in Sub-Saharan Africa could be covered by new investments of \$150 million per year through the year 2020.

In addition to government commitments, private philanthropy is helping to address these gaps by supporting drug delivery and surveillance programs, as well as research and development into new medicines, diagnostics and other health tools. [The END Fund](#), founded shortly after the London Declaration, has raised over \$75 million to target the five most common NTDs, helping to treat over 145 million people around the world.

Political Commitment

Strong leadership from affected countries is vital to sustaining progress against NTDs, particularly in the face of shifting economic climates and competing health priorities. Despite these challenges, some countries are increasing financing for NTD programs and integrating them into national health systems. Among other countries, Ethiopia has made significant strides in fighting trachoma by including progress against the disease as a target in its national health plan, providing significant domestic funding, participating in the Global Trachoma Mapping Project and training surgeons to conduct eye-lid surgeries to correct the effects of trachoma.

“Ethiopia is fully committed to realizing ambitious, yet achievable, elimination targets for trachoma and other NTDs with proactive program coordination,” said H.E Professor Yifru Berhan Mitke, Ethiopian Minister of Health. “An increased direct program financial contribution by the government to NTDs, as high as 3 million USD by 2016, is a big step forward in alleviating the burden and stigma of these diseases.”

New Tools and Innovations

To meet control and elimination targets, more research and development is needed to provide NTD programs with improved tools to prevent, detect and treat the diseases. Promising new therapies are in the pipeline: A new three-drug regimen for LF known as triple therapy has the potential to dramatically accelerate the pace of elimination in affected countries, and is currently in large-scale safety trials in India.

R&D organizations such as PATH and partnerships like DNDi and the Global Health Innovative Technology Fund have catalyzed the development of better and more cost-effective tools. These innovations, which include new drugs and rapid diagnostic tests for sleeping sickness and river blindness, are especially critical in the low-resource settings most burdened by NTDs. Several new vector control tools are under development and being piloted to address the growing problem of diseases transmitted by *Aedes* mosquitoes.

The [Global Partners Meeting on Neglected Tropical Diseases](#) will be hosted by the World Health Organization on 19 April 2017. From 20-22 April, Uniting to Combat NTDs and the global NTD community will host the [NTD Summit](#), which will feature technical discussions on the best strategies to reach the NTD control and elimination goals.

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About Uniting to Combat Neglected Tropical Diseases: *Established in 2012, [Uniting to Combat NTDs](#) is a group of organizations committed to achieving the WHO's 2020 goal to control and eliminate 10 NTDs as laid out in the London Declaration. By working together, Uniting to Combat NTDs aims to chart a new course toward health and sustainability among the world's poorest communities.*

The 10 diseases covered by the London Declaration include onchocerciasis (river blindness), Guinea worm disease, lymphatic filariasis (elephantiasis), blinding trachoma, schistosomiasis, soil-transmitted helminths, leprosy, Chagas disease, visceral leishmaniasis and human African trypanosomiasis (sleeping sickness). To find out more about the work of Uniting to Combat NTDs and to learn more about NTDs, please visit our [website](#).

About the London Declaration on Neglected Tropical Diseases: *The [London Declaration on NTDs](#), launched on 30 January 2012, is a joint commitment to control, eliminate or eradicate NTDs, signed by WHO, 13 pharmaceutical companies, donor and endemic country governments, the Bill & Melinda Gates Foundation and the World Bank.*

APPENDICES

I. Additional Partner Remarks

“We’re proud to celebrate the progress made by all partners on the fifth anniversary of the London Declaration. MSD is committed to building on our 30-year history of partnership through the Mectizan Donation Program to bring treatments to those afflicted by river blindness and lymphatic filariasis – contributing to the goal of eliminating NTDs globally.” – **Ken Frazier, Chairman and CEO, MSD**

“The impressive progress made toward eliminating blinding trachoma is a testament to the power of collaboration in helping to address neglected tropical diseases. Pfizer is working with more than 100 public and private partners to

advance the World Health Organization's goal of eliminating trachoma by 2020, so that the 185 million individuals in affected communities have the opportunity to live the healthiest life possible." – **Ian Read, CEO, Pfizer**

"We are very pleased to see the role that our donations have played over the last five years, contributing to the work of the World Health Organization (WHO) to eliminate or eradicate visceral leishmaniasis in endemic countries such as India, Nepal and Bangladesh. Last year we renewed this long-standing partnership, allowing the WHO to further expand and reinforce surveillance and control of leishmaniasis well beyond South-East Asia." – **John Milligan, President and CEO, Gilead**

"We continue working hand-in-hand with our partners to achieve zero transmission of leprosy. Our common goal is to make leprosy history." – **Joe Jimenez, CEO, Novartis**

"Sanofi has a long-standing commitment to reduce the burden of neglected tropical diseases. Since 2001, the company and WHO have established a partnership encompassing provision of drugs and funding to support surveillance programs. Sanofi has played and will play a key role in the elimination of sleeping sickness." – **Olivier Brandicourt, CEO, Sanofi**

"We are delighted to have contributed to the positive progress set out in today's report by donating over seven billion tablets to 91 countries to date to help eliminate lymphatic filariasis (LF) and control intestinal worms, diseases that prevent people from working and lock families in poverty. This has helped Togo to become the first African country to eliminate LF. The Uniting to Combat NTDs coalition is a big and bold initiative that has been instrumental in coordinating and accelerating action against diseases which typically affect people in remote, rural and marginalised communities. GSK will continue to play an active role by donating medicines, investing in research and helping strengthen health infrastructure to achieve the 2020 goals." – **Phil Thomson, President of Global Affairs, GSK**

"The heavy burden of neglected tropical diseases for patients and society can only be reduced through the concerted efforts of many parties. This is why we joined forces with many partners and support the development of a pediatric formulation of our compound Nifurtimox to help newborns and children to have the best chance to be cured from Chagas disease. And together with the Drugs for Neglected Diseases *initiative* we are developing Emodepside as an innovative treatment for river blindness." – **Dieter Weinand, Member of the Board of Management of Bayer AG and President of Bayer's Pharmaceuticals Division**

"For all of us at Johnson & Johnson, there is nothing more rewarding than delivering on commitments that protect the health of millions of individuals, families, and communities worldwide. We are pleased to have donated over 1 billion doses of mebendazole to date as part of our longstanding commitment to Children Without Worms and developed a new chewable form, recently approved by the FDA, for children too young to swallow. As signatories of the London Declaration on Neglected Tropical Diseases five years ago, we are heartened by the progress we see as a result of our collective efforts. It clearly shows how multiple stakeholders—scientists, industry, academia, government, civil society—coming together to work on a global health challenge can move the needle and make the difference for all of humanity." – **Alex Gorsky, CEO and Chairman, Johnson & Johnson**

"The London Declaration five years ago undoubtedly gave a new impulse to the fight against the most neglected diseases. The fight is far from over. We are yet to see the breakthroughs that will bring newer, safer, better drugs, diagnostics or vaccines to the most neglected. Collectively, we need to sustain our scientific, political and financial commitments, particularly on research and development, to provide neglected people with the modern health technologies needed to sustain elimination of many of these diseases." – **Bernard Pécou, CEO, DNDi**

"All of us at the Uniting to Combat NTDs Support Centre are very proud to be associated with this incredible partnership, working hand in hand, to end the suffering caused by these horrible diseases. We take this opportunity to congratulate every single person in the Uniting family who has contributed to the tremendous progress of the London Declaration over the last five years. We are honored to be doing our part and to be working with all the partners in this truly unique global partnership. We look forward to yet more success in the years ahead." – **Thoko Elphick-Pooley, Director, Uniting to Combat NTDs Support Centre**

"Over the last five years, I have been inspired and humbled by the private philanthropists who have joined us to invest in NTDs. Not only have they provided much needed capital for NTD programs, but many have become champions for the cause, involving their families and networks to ensure that together, we see an end to these diseases." – **Ellen Agler, CEO, The END Fund**

"Together with our founders Jimmy and Rosalynn Carter, the Carter Center holds that everyone deserves adequate health care regardless of economic status. Neglected tropical diseases mainly afflict the poor and politically marginalized, but we are committed to making sure they are neglected no more so people can improve their own lives. We are proud to be a partner in this important effort." – **Ambassador (ret.) Mary Ann Peters, CEO, Carter Center**

"The NNN is proud of the remarkable progress made against NTDs, and excited that our network has grown to encompass 60 organizations in more than 100 countries and mobilized over 200 million euros to support NTD programs. By developing the BEST Framework, a comprehensive approach to fighting NTDs that goes beyond the health community, we are catalyzing new approaches to how NTDs interacts with other priorities like WASH and vector control. We hope partners will use it to drive progress toward the NTD control and elimination targets and ultimately the SDGs." – **Wendy Harrison, Chair, Neglected Tropical Disease NGDO Network (NNN)**

"For more than two decades, Vestergaard has dedicated its innovative platform to product development and partner engagements aimed at reducing the burden of neglected tropical diseases. This includes extensive work to decrease the incidence of sleeping sickness. Our ZeroFly Tiny Targets are an important tool and we pledge to scale up our donation of these targets, moving towards 100% as we near elimination. We're committed to stand with our partners to see eradication of Human African Trypanosomiasis become a reality." – **Mikkel Vestergaard, CEO, Vestergaard**

III. Table of Disease-Specific Progress

Disease	Progress
Lymphatic Filariasis (LF)	<p>Significant progress has been made to interrupt LF transmission and alleviate the suffering of affected populations.</p> <ul style="list-style-type: none"> ● In the last year alone, eight countries – Cambodia, Cook Islands, Maldives, Niue, Sri Lanka, Vanuatu, Marshall Islands and Togo – eliminated LF as a public health problem, and 10 other countries are waiting on surveillance results to verify elimination. ● The total number of people requiring MDA for LF decreased from 1.4 billion in 2011 to 947 million in 2015. ● Coverage for LF treatment reached 59.3% by the end of 2015, a 56% increase from 2008. ● Three companies donate drugs to treat and prevent LF: Eisai (diethylcarbamazine, or DEC), GlaxoSmithKline (albendazole) and MSD (ivermectin).
Guinea worm disease	<p>Guinea worm disease is on track to be the second human disease in history to be eradicated.</p> <ul style="list-style-type: none"> ● Guinea worm disease, which 30 years ago afflicted more than 3 million people in 20 countries, is on the brink of eradication, with just 25 cases in three countries.
Onchocerciasis (river blindness)	<p>Onchocerciasis has been eliminated in nearly all of the Americas.</p> <ul style="list-style-type: none"> ● Guatemala (2016), Mexico (2015), Ecuador (2014) and Colombia (2013) have all recently been declared "onchocerciasis-free." The final step toward making the entire region free of the disease is to eliminate it among Amazonian indigenous communities living along the Brazil-Venezuela border. 95% of people who live in onchocerciasis-endemic areas in the Americas no longer require treatment. ● Onchocerciasis control programs achieved 62% coverage in 2015. ● MSD donates ivermectin to treat onchocerciasis.

Schistosomiasis	<p>There has been notable progress against schistosomiasis, particularly in Africa.</p> <ul style="list-style-type: none"> • 74.3 million people received treatment for schistosomiasis in 2015, representing a fourfold increase in coverage since 2008. • In 2015, 87% of countries were entirely mapped for schistosomiasis. Only Angola, Central African Republic, Ethiopia, South Africa and South Sudan have areas that still need to be surveyed. • Merck KGaA donates praziquantel to treat schistosomiasis.
Soil-transmitted helminths (STH)	<p>There has been a steady increase in treatment coverage for STH, particularly among children at high risk of infection.</p> <ul style="list-style-type: none"> • The total number of STH treatments reported globally increased from 261 million in 2010 to 447 million in 2014. • Rates of STH treatment coverage for children have increased from just 10% reached in 2003 to 59% in 2015. The WHO is optimistic that the global target of 75% coverage will be met by 2020. • Since 2011, 29 countries in Africa have achieved greater than 75% coverage for STH among preschool-aged children, and 19 more countries have achieved the same level of coverage for school-aged children. • GlaxoSmithKline and Johnson & Johnson donate albendazole and mebendazole, respectively, to treat STH. • Johnson & Johnson has developed and recently got approval for a new chewable form of mebendazole for children too young to swallow.
Trachoma	<p>Improved access to data and strong country commitments have paved the way for significant progress against trachoma.</p> <ul style="list-style-type: none"> • By the end of 2016, Oman, Morocco and Mexico were validated as having eliminated trachoma as a public health problem. China, the Gambia, Ghana, Iran, Laos and Myanmar have also reported reaching elimination targets. • The Global Trachoma Mapping Project, completed in December 2015, has provided reliable epidemiological data to help tackle the disease. The initiative identified that interventions are required to eliminate trachoma for 100 million people living in areas that were previously categorized as “suspected endemic” – effectively doubling the population already known to require trachoma interventions. With this new data, countries can more precisely determine populations most at risk for the disease – and, conversely, can identify where resources can be saved. • Pfizer donates azithromycin to treat trachoma, and doubled its donation in the last two years in response to the improved mapping data.
Chagas	<p>Overall, there has been progress in reducing Chagas disease transmission in Latin America.</p> <ul style="list-style-type: none"> • In 2015, all Latin American countries achieved universal blood screening for Chagas disease among blood donors, greatly reducing the risk of transmission by blood transfusion. • The total number of people treated with either benznidazole or nifurtimox for Chagas disease has more than tripled in the last three years. • The interruption of vector-borne transmission of Chagas disease in people’s homes has been verified in in most of Latin America. • Bayer donates Nifurtimox to treat Chagas.
Human African Trypanosomiasis (HAT, or sleeping sickness)	<p>Sleeping sickness could be eliminated as a public health problem by 2020 if progress is sustained.</p> <ul style="list-style-type: none"> • In 2015, there were fewer than 3,000 sleeping sickness cases reported worldwide, down from approximately 10,000 in 2009 and nearly 40,000 in 1998. • The number of people at high or very high risk of sleeping sickness has significantly decreased, from 6.3 million in 2000-2004 to 1.2 million in 2010-2014. • Bayer donates Suramin and Sanofi donates Eflornithine, Arsobal and Pentamidine to treat HAT.

<p>Leprosy</p>	<p>Since the 1980s, when Multidrug Therapy (MDT) became available to interrupt leprosy transmission, the global burden of leprosy has been reduced by 99%.</p> <ul style="list-style-type: none"> ● New cases of leprosy have declined in eight of the last nine years. ● Novartis donates Rifampin, Clofazimine and Dapsone to treat leprosy.
<p>Visceral Leishmaniasis (VL, or Kala Azar)</p>	<p>Thanks to global NTD efforts, the burden of VL in South-East Asia has fallen sharply.</p> <ul style="list-style-type: none"> ● There was an 82% reduction in the number of VL cases in Bangladesh, India and Nepal from 2007-2015. ● Since 2012, the incidence of reported VL cases in Bangladesh, India and Nepal decreased by 67%, 61% and 46% respectively. ● Gilead donates AmBisome to treat VL.