Open letters by AIDS and TB organisations calling for access to a new TB drug and a new TB diagnostic

By *moderator*
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Today the 41st World Lung Conference opens in Berlin. This is the main annual global TB conference. We are pleased that after decades of very little technological progress in the diagnosis, treatment and prevention of TB, there are now important technological advances. There are promising new TB drugs in the pipeline and a new diagnostic that detects TB in less than 2 hours. But with these advances comes the challenge of ensuring that people most in need of them across the world can access them.

Hence over 40 organisations working in HIV or TB have written two open letters. One is to Tibotec calling for accelerated access to the new experimental TB drug, TMC207. The other is to Cepheid, calling for steps to be taken to make its Gene Xpert diagnostic more accessible.

Please see below letters to Cepheid and Tibotec.

11 November 2010

Mr. John L. Bishop
CEO
Cepheid
904 Caribbean Drive
Sunnyvale, CA 94089
USA

By fax and email: +1-408-541-4192 and john.bishop@cepheid.com

By hand to Cepheid at the 41st Union World Conference on Lung Health in Berlin

Dear Mr Bishop

RE: ACCESS TO THE CEPHEID GENE XPERT® MTB/RIFN IN AREAS WITH HIGH TB BURDEN

We represent organisations working to make treatment and prevention services accessible to people with TB and HIV.

As you are aware, the Xpert® MTB/RIF is a TB diagnostic machine that detects active TB and rifampicin resistance within two hours. In a recent study conducted in four countries the Xpert® MTB/RIF achieved a sensitivity of 98% on sputum that was smear and culture positive. On culture-positive, smear-negative sputum, the Xpert® MTB/RIF achieved a sensitivity rate of 73%, but if the test was repeated this rose to 85% and if it was repeated yet again, it rose to 90%. Specificity was over 99%. Furthermore, the Xpert® MTB/RIF detected a significant number of TB cases diagnosed by clinicians but not detected by culture. Detection of rifampicin resistance was also highly sensitive and specific.1

For patients accessing clinics that are able to make use of appropriately equipped diagnostic facilities with reliable

electricity supplies, this test has the potential to dramatically shorten diagnostics time for drug-susceptible and drug-resistant TB. While not quite a point-of-care test, this is nevertheless an important advance in TB diagnostics.

We congratulate Cepheid, the Foundation for Innovative New Diagnostics (FIND), the U.S. National Institute of Allergy and Infectious Diseases (NIAID, for grant no. AI52523), the Bill and Melinda Gates Foundation, and the U.S. Department of Defense Advanced Research Project Agency, for their role in the development of this diagnostic test.

However, the challenges to making this device widely available in high-burden TB countries must now be overcome. One of these challenges is the reported price of the machine and the non-reusable cartridges required for each test. We understand that currently Cepheid is intending to sell the smallest machine that takes only four cartridges for approximately $20,000 to $30,000. We further understand that each cartridge will sell for $20 to $30. Because the machine will need to be calibrated annually to ensure its accuracy, a system needs to be developed to facilitate and monitor this regular maintenance to machines placed around the world. If this is not implemented there is a danger that the investment made in the development and scale up of the Xpert® MTB/RIF will not yield the desired accurate results.

These prices are extremely high and unless they are reduced significantly they will constitute a significant barrier to access for developing countries, especially in sub-Saharan Africa. We have been informed that Cepheid is considering differential pricing and/or price reductions based on sales, but no details of this have been released.

We therefore call on CEPHEID to increase access to this diagnostic test by taking steps to make it more affordable and ensuring access to ongoing training as needed and required maintenance procedures. This could be done, for example, by making substantial price reductions or allowing competitive manufacturers to make and sell the device for a reasonable royalty fee. It can be further facilitated by complementing online methods to train clinic staff to calibrate with a good network of phone and in-person customer service to address maintenance needs and problem solving.

Given the urgent need to improve TB diagnostics and to make this device available worldwide, we ask you to respond positively to this letter by World AIDS Day, 1 December 2010.

Yours sincerely

Vuyiseka Dubula on behalf of **Treatment Action Campaign, South Africa**

Mark Harrington, Javid Syed, and Claire Wingfield on behalf of **Treatment Action Group, USA**

Polly Clayden on behalf of **HIV i-Base, UK**

Francois Venter on behalf of **Southern African HIV Clinicians Society**

Jonathan Berger on behalf of **SECTION27 incorporating the AIDS Law Project, South Africa**

Wim Vandevelde on behalf of **European AIDS Treatment Group**

Paula Donovan and Stephen Lewis on behalf of **AIDS-Free World, USA**

Asia Russell on behalf of Health GAP (Global Access Project), **Uganda**

Tendayi Westerhof on behalf of **Public Personalities Against AIDS Trust, Zimbabwe**

Kassahun Argaw on behalf of **Ethiopia Treatment Access Movement, Ethiopia**

Donna J Barry, Policy and Advocacy Director on behalf of **Partners In Health, USA**

Lois Eldred on behalf of **Consortium to Respond Effectively to the TB AIDS Epidemic (CREATE), USA**

Paula Akugizibwe on behalf of **ARASA, Namibia**

Nelson Juma Otwoma on behalf of the**National Empowerment Network of PLHAs in Kenya (NEPHAK), Kenya**

Richard Elliott on behalf of the**Canadian HIV/AIDS Legal Network, Canada**

Elijah Amooti on behalf of **The African Eye Trust**

Denise Hunt on behalf of the **AIDS Consortium, South Africa**

Carly Tanur on behalf of **Mamelani Projects, South Africa**

Sharon Gelman on behalf of **Artists for a New South Africa, USA**

Francisco Rosas on behalf of **Vivir. Participacion, Incidencia y Transparencia, A.C. Mexico**

Lucy Chesire on behalf of **TB ACTION group, Kenya**

Francis George Apina on behalf o**f NETMA+, Kenya**

Benjamin Dzivenu on behalf of **Hope Care Foundation, Ghana**

Kennedy Mupeli on behalf of **Centre for Youth of Hope ? CEYOHO, Botswana**

Andy A. Kings on behalf of **Shalom International, Senegal**

Wilson Zulu on behalf of **Zambia Association for the Prevention of HIV and Tuberculosis (ZAPHIT)**

Simão Cacumba M Faria on behalf of**SCARJoV-Association for Reintegration of Youth Children in Social Life, Angola**

Dr.Alita Ram on behalf of **Association For Christian Thoughtfulness, India**

Dr. Noor Ahmad Baloch on behalf of **NTP Pakistan**

Sarah Zaidi on behalf of the **International Treatment Preparedness Coalition, Thailand**

David Haerry on behalf of **Positive Council Switzerland**

Savita Luka, Shabab Alam, David Thapa, Simon Lobo, Vijay Gupta, Sumaiya Nazir on behalf of **Misbah, India**

Meeta Biswas, Shashi Bharti, Rajwinder and Beena Akhtar on behalf of **Naz Foundation, India.**

Patricia Asero Ochieng on behalf of **Network of African People Living with HIV, Eastern African Region**

Paul Kasonkomona of behalf of **Civil Society Health Forum (CSHF), Zambia**

Micahel Gwaba on behalf of the **Community Initiative for Tuberculosis, HIV/AIDS & Malaria plus related diseases (CITAM+), Zambia**

Emmanuel Trenado on behalf of **Plus, France**

Xavier Franquet on behalf of **Grupo de Trabajo sobre Tratamientos del VIH ? gTt, Spain**

Luís Mendão on behalf of**GAT - Grupo Português de Activistas sobre Tratamentos de VIH/SIDA, Portugal**

Sergio Souza Costa on behalf of **Gestos: HIV+, Communication and Gender Issues and The Latin American and Caribbean Council of AIDS Service Organizations ? LACCASO**

Batul Balasinorwala on behalf of **Action Project, Global Health Advocates India**

Prisca Munonyara on behalf of **AIDS Counselling Trust (ACT), Zimbabwe**

Debbie Mathew on behalf of the **AIDS Foundation of South Africa, South Africa**

Alessandra Cerioli on behalf of **LILA - Lega Italiana per la Lotta all'Aids - Italian League to Fight Aids, Italy**

Beate Ramme-Fuelle on behalf of **Action against AIDS Germany**

Mike Mandelbaum on behalf of **TB Alert, United Kingdom**

Cc: Dr. Giorgio Roscigno
FIND
Avenue de Budé 16
1202 Geneva, Switzerland

By fax and email: + 41 (22) 710 05 99 and giorgio.roscigno@finddiagnostics.org

1Boehme CC et al., Rapid Molecular Detection of Tuberculosis and Rifampin Resistance. N Engl J Med 2010; 363:1005-1015. 9 September 2010

11 November 2010

Dr. Paul Stoffels, M.D.
Company Group Chairman
Global Research and Development, Pharmaceuticals
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
PStoffels@its.jnj.com

Mr Glenn Mattes
President
Tibotec Therapeutics
1125 Trenton-Harbourton Road
Titusville NJ 08560
GMattes@its.jnj.com

By email and by hand to Tibotec representatives at the 41st Union World Conference on Lung Health in Berlin

Dear Dr. Stoffels and Mr. Mattes

Re: EXPANDED ACCESS TO TMC207

We represent organisations working to make high-quality treatment and prevention services accessible to people with TB and HIV.

As you are aware, TMC207 is an anti-TB drug discovered and developed by Tibotec, a subsidiary of Johnson& Johnson. It is currently in a phase IIb trial for treatment of multi-drug-resistant TB (MDR-TB). Early results from this trial indicate that patients with MDR TB who take this drug plus standard background therapy convert to sputum-negative faster than patients taking only standard background therapy.1

We understand that new and promising data on TMC207 will be presented at the World Lung Conference starting today in Berlin.

We congratulate Tibotec for developing the first TB drug in a new class in four decades. Although TMC207 needs further testing, it is likely to be a substantial advance in the treatment of TB.

It is not yet clear what the timeline for regulatory approval of TMC207 is likely to be, nor in what countries the company will file for approval, in what sequence, or whether accelerated or conditional approval will be granted by stringent regulatory authorities based on the ability of TMC207 to address an urgent unmet medical need ? in this case, the global pandemic of multi-drug resistant (MDR) tuberculosis. However, in the meanwhile, patients with MDR TB are at high risk of death, especially if they become resistant to either a fluoroquinolone or one of the injectables amikacin, capreomycin, or kanamycin (pre-extensively drug resistant or XDR-TB), or resistant to both a fluoroquinolone and an injectable (full XDR-TB). For these patients, TMC207 represents a lifeline, a drug that will reduce their risk of dying and has demonstrated the potential to significantly reduce the extremely long treatment period for patients with MDR and XDR TB.

We therefore call upon Tibotec and Johnson & Johnson to take urgent steps to make TMC207 available as part of an expanded access programme. There are risks to this approach. There is the possibility that TMC207 might not be approved. There is also the risk that MTB strains will emerge which become resistant to TMC207. Nevertheless, we believe that these risks can be managed by appropriate program design and patient selection. These risks are small compared to the morbidity and mortality risks of MDR and XDR TB patients. Furthermore there are other TB drugs in the pipeline, such as OPC-67683, that can help avoid the problem of adding a single drug to failing regimens? especially if, as may be possible, both drugs become available through expanded access, accelerated or conditional approval, and early roll-out into programmatic settings, within a year of each other.

Since 1985, most of the anti-HIV drugs which were eventually approved by stringent regulatory authorities have been made available in North America and Europe to individuals who needed a new agent to construct a viable treatment regimen, who were ineligible for controlled clinical trials, or who were intolerant or failing on approved therapies. Tibotec itself has participated in several expanded access programs for its antiretroviral drugs such as darunavir and etravirine. Most recently Tibotec initiated an open-label non-randomized study of TMC207 as part of an individualized regimen for the treatment of MDR-TB among 225 individuals recruited at 29 sites worldwide including sites in China, Estonia, Kenya, South Korea, Latvia, Peru, the Philippines, the Russian Federation, South Africa, Thailand, Turkey and Ukraine.

This is an important open-label study[2] that will advance knowledge and provide access to TMC207 for 225 individuals with MDR-TB. However, according to the Stop TB Partnership and the World Health Organization (WHO), in 2008 ? the last year for which complete data are available ? an estimated 440,000 individuals worldwide developed MDR-TB and 150,000 people died of the disease. Just seven percent (7%) or 29,423 of these cases were diagnosed and notified to public heatlh authorities. A subset of countries reported on treatment outcomes for MDR-TB patients who were diagnosed and started treatment in 2006. Treatment success rates were 60% overall, with higher rates at quality assured sites.[3]

Expanded access to TMC207 should be made available to individuals with MDR-, pre-XDR-, and XDR-TB who are receiving treatment at well-functioning treatment programs. Such programmes should have the capacity to support treatment administration, monitor and assist patient adherence, provide access to drug susceptibilty testing and provide quality assured companion drugs available to ensure that the TMC207-containing regimen has sufficient bactericidal activity to avoid the development of resistance to any of the drugs. Implementing expanded access programmes will require that Tibotec takes steps to support regulatory authority authorisation for an as yet unapproved drug (such as, for example, Section 21 authorisations in South Africa).

Expanded access to life-saving experimental treatments with appropriate safety and activity profiles is increasingly recognized as industry best practice as in the example of HIV. We believe it should be accepted practice for MDR and XDR TB as well.

We look forward to your positive response to this letter by or before World AIDS Day, 1 December 2010.

Yours sincerely

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Mark Harrington, Javid Syed, and Claire Wingfield on behalf of **Treatment Action Group, USA**

Polly Clayden on behalf of **HIV i-Base, UK**

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Beate Ramme-Fuelle on behalf of **Action against AIDS Germany**

Mike Mandelbaum on behalf of **TB Alert, United Kingdom**

Cc: J&J Global Communications
Mailstop E1756
920 Route 202
Raritan, NJ 08869, USA
GlblPharmaRDCom@prdus.jnj.com

1Diacon AH et al. The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis. N Engl J Med 2009; 360:2397-2405, 4 June 2009; Diacon AH, et al. Final results from stage 1 of a double-blind, placebo-controlled trial with TMC207 in patients with multi-drug resistant (MDR) tuberculosis (TB), Abstract L1-521a. 2010 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 12-15 September 2010, Boston, MA.

2ClinicalTrials.gov ID # NCT00910871; Tibotec # TMC207-TiDP13-C209

3Data from World Health Organization. Multidrug and extensively drug-resistant TB (M/XDR-TB) 2010 global report

on surveillance and response. http://whqlibdoc.who.int/publications/2010/9789241599191_eng.pdf, p. 23.
