Bill and Melinda Gates

Bill & Melinda Gates Foundation
PO Box 23350
Seattle, WA 98102

14 December 2011

Dear Mr and Mrs Gates,

We write as people with HIV and community activists with serious and unresolved concerns about the proposed clinical trial comparing stavudine at 20 mg to tenofovir.[1]

Although we are broadly very supportive of dose optimisation strategies, we do not support this trial; we do not think that the Bill and Melinda Gates Foundation should support it; nor do we think it should proceed. Several of us have discussed this with your representatives both formally and informally over the past months. Those of us who met with your representatives on 19 July 2011 at the International AIDS Society conference in Rome received no response to the concerns we raised. We summarise our objections as follows:

1. Stavudine is more toxic than tenofovir, and for this reason, it is an inferior option. The proposed trial aims to establish virological non-inferiority, which is a moot point, given the severe adverse events associated with stavudine. Considerable evidence supports the use of tenofovir over stavudine; regulatory bodies and the World Health Organization (WHO) have turned away from the drug. In 2004, stavudine was removed from the list of preferred first-line antiretroviral drugs recommended by the US Department of Health and Human Services (DHHS).[2] Starting in 2006, the WHO recommended that countries start moving away from stavudine, and in 2009 recommended that the drug be phased out in first-line antiretroviral treatment (ART) programmes.[3] Earlier this year, the European Medicines Agency (EMA) revised the indication for stavudine, noting, "…that the use of the medicine should be severely restricted in both adults and children... Prescribers are reminded of the severe side effects seen with Zerit [stavudine] and should only use the medicine when other appropriate treatments are not available. Patients being treated with Zerit should be assessed frequently and switched to appropriate alternatives as soon as possible."[4]

Médecins Sans Frontières (MSF)/ Doctors Without Borders have provided further compelling evidence of stavudine's toxicity in an operational setting. In a Lesotho cohort, the authors found that, "…for patients on stavudine, the risk of a toxicity-driven regimen switch was almost six times higher than tenofovir."[5] The high incidence of adverse events among patients on stavudine-containing first-line regimens has also been documented in a larger prospective study in South Africa.[6] In that study 30% of patients had to switch from stavudine-based to non-stavudine based regimens within three years.

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[1] A randomised, double-blind study to demonstrate non-inferiority of stavudine (20 mg BID) compared with tenofovir (300 mg QD) co-administered with lamivudine and efavirenz in antiretroviral-naive patients over 96 weeks. If funded and approved, the trial is anticipated to start early 2012.

[2] Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. 29 October 2004. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL10292004002.pdf

[3] WHO Rapid Advice: Antiretroviral therapy for HIV infection in adults and adolescents. November 2009. http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf, page 10

[4] EMA 17 February 2011. EMA/127094/2011. EMEA/H/C/000110/R/79. Questions and answers on the review of Zerit (stavudine): Outcome of a renewal procedure: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/human/000110/WC500102227.pdf.

[5] Adjusted hazard ratio: 5.43, 95% confidence interval: 3.31 to 8.91. Bygrave H et al. 2011. Implementing a tenofovir-based first-line regimen in rural Lesotho: clinical outcomes and toxicities after two years. J Acquir Immune Defic Syndr. 2011 Mar 1;56(3):e75-8. http://www.ncbi.nlm.nih.gov/pubmed/21164354

[6] Menezes et al. A longitudinal study of stavudine-associated toxicities in a large cohort of South African HIV infected subjects. BMC Infectious Diseases 2011, 11:244 doi:10.1186/1471-2334-11-244

For good reason, tenofovir has become the gold standard for today's first-line antiretroviral therapy. Its introduction in developing countries is an important step to slowly bringing treatment in poor countries in line with rich ones. As WHO and all countries are phasing out stavudine, this study will send a confusing message, and it may slow down this transition while countries wait for the results.

There is no prospect that stavudine 20 mg is a better option than tenofovir. The stavudine parallel track programme, in which over 10,000 patients were randomised to receive 40 (30) mg or 20 (15) mg between October 1992 and February 1994, showed a higher incidence of neuropathy in the high-dose arm (21%). Nonetheless, the incidence of neuropathy observed in the lower dose arm was also unacceptably high (15%).[7]

The stavudine 20 mg study is not being proposed in any developed country. Instead it is planned to include only middle and lower-income developing countries. Patients enrolling in this trial risk being randomised to receive treatment that may be less effective and is more toxic than the current standard of care. There is therefore no good reason why a properly informed patient should want to enrol in this study.

2. The poor tolerability of stavudine limits therapeutic durability. A person has the best chance at successful treatment with their first-line regimen, making it critical that the medicines are as tolerable as possible. A tolerable first-line regimen enhances therapeutic durability by helping people adhere to treatment, and delays their need to switch to more costly second-line regimens, which are complicated for patients, health workers and from an operational standpoint.

3. Stavudine's side effects cut into stavudine's savings on cost. A study just published by MSF shows that inpatient care and essential drug costs were higher for people on stavudine than those on tenofovir in a cohort in rural Lesotho. According to MSF's cost-effectiveness study of switching from stavudine or zidovudine to tenofovir-based first-line regimens in Lesotho, the tenofovir-containing regimen generated higher life years and QALYs than zidovudine or stavudine-based treatment.[8] As the costs of tenofovir and especially efavirenz drop, the cost benefit to patients and to health systems will become clearer. Since the study was completed, the global best price of efavirenz – which partly drives tenofovir costs – has almost halved ($97 ppy in 2009 to $52 today).

4. Stavudine can compromise second-line options. When someone does fail their first-line regimen, the longer they remain on stavudine – which is likely in a context with limited access to viral load monitoring – the more their second-line options are compromised. Unlike stavudine, tenofovir does not confer thymidine analogue mutations (TAMs); people taking tenofovir can stay on a failing regimen much longer without compromising efficacy of zidovudine and thus second-line therapy.

5. Stavudine's long-term toxicity question will not be answered by this trial. The proposed 20 mg stavudine dose might be acceptable in a short-term 48- or even 96-week virologic endpoint study (although Bristol-Myers Squibb studied and rejected 20 mg BID). But, because mitrochondrial toxicity is both dose and time dependent, many of stavudine's most serious side effects (such as peripheral neuropathy and lipoatrophy) would not necessarily emerge until after such a study was completed. This study does not include monitoring of surrogate markers for mitochondrial toxicity, so it cannot shed light on the incidence of this serious adverse event.

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[7] Anderson R et al. Design and implementation of the stavudine parallel track programme. Comparison of safety and efficacy of two doses of stavudine in a simple trial in the US parallel track programme. J Inf Dis. 1995; 171:118-22.

[8] Jouquet et al. Cost and cost-effectiveness of switching from d4T or AZT to a TDF-based first-line regimen in a resource limited setting in rural Lesotho. JAIDS Publish Ahead of Print. DOI: 10.1097/QAI.

Your representatives have agreed that this important question about longer-term toxicity will not be answered in the trial, thus raising the serious issue that the trial will not be able to answer the primary policy question which drives it - whether long-term 20 mg stavudine BID is as good as tenofovir QD in first-line ART regimens for use in public health programmes in resource-limited settings.

6. Stavudine must be taken twice a day, compared to tenofovir's once-daily dosing. A twice-daily dosing regimen (as with stavudine 20 mg) does not have the simplicity of a once-daily fixed-dose combination (as with tenofovir). People are more likely to adhere to simpler regimens and therefore are more likely to have better treatment outcomes, as well as stave off resistance that requires more complex and expensive second-line regimens.

7. A tenofovir-based regimen is recommended for HIV/hepatitis B (HBV) coinfection, because stavudine has no activity against HBV and resistance to lamivudine is inevitable. While HIV/HBV co-infection is an exclusion criterion for this trial, it may encourage persistent use of a suboptimal regimen for HIV/HBV co-infected people. Screening for HBV is not routinely performed prior to initiation of ART in most resource-limited settings, yet HBV is endemic. For example in South Africa, an estimated 5% of HIV-positive people are HBV co-infected[9]. Giving a stavudine/lamivudine-based regimen to HIV/HBV co-infected people will create lamivudine resistant HBV in this population (90% at four years)[10]. Continuing lamivudine in the context of HBV drug resistance may lead to hepatitis flares; these flares can cause serious liver damage, and are potentially life-threatening. Researchers are also concerned about the transmission of drug-resistant HBV that may not be preventable by currently available HBV vaccines, a potential public health catastrophe.

8. Stavudine-related cost savings may become irrelevant by the trial's end. The rationale for this trial is to lower treatment costs, as stavudine is currently cheaper than its alternatives. However, the price of alternatives, notably tenofovir, has come down dramatically in the last several years, and is expected to decrease further as demand increases. According to MSF's annual ARV pricing report, tenofovir is now cheaper than zidovudine, with the price of single-drug tenofovir having decreased by 52% from 2008 to 2011, and the price of the triple fixed-dose combination of tenofovir, lamivudine and efavirenz having decreased by 53% to US$173 per person per year over that same time period.[11] Because the stavudine 20mg 96-week efficacy trial is expected to be completed at the earliest by 2014-2015, and would need to be followed by a larger, longer, perhaps five-year field effectiveness trial to determine longer-term tolerability, the drug may not be available for use at the new dose until possibly even 2020. It is thus likely to take nine years from now for there to be enough evidence that 20mg stavudine is safe and non-inferior to tenofovir, and could be used to replace tenofovir in first-line regimens.

If current price trends continue, it is likely the anticipated cost savings associated with stavudine will be overtaken by expected further price reductions for tenofovir, by the time stavudine 20mg were ready for use. It is worth noting that a three-drug one-pill-once-a-day regimen containing efavirenz and tenofovir is now priced at roughly half of what stavudine-based Triomune cost when it was first introduced a decade ago.

Further, even greater potential savings could be achieved if the tenofovir prodrug GS 7340, now in phase II by Gilead Sciences, is approved at a low milligram dose. Results will be

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[9] Communication Dr Mark Sonderup, Division of Hepatology, University of Cape Town.

[10] Benhamou Y et al. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. Hepatology. 1999;30:1302-1306.

[11] Untangling the Web of Antiretroviral Price Reductions, 14th Edition. July 2011. Médecins Sans Frontières Campaign for Access to Essential Medicines

available within a similar time frame to those from the 96-week stavudine 20 mg trial. A recent announcement by Gilead of an agreement with Tibotec to develop an FDC of darunavir, emtricitabine, GS 7340 and cobicistat with “less than one tenth of the amount of the 300 mg of tenofovir disoproxil fumarate contained in Viread and Truvada" suggests that this is feasible.[12] Chimerix Inc. also has a promising tenofovir pro-drug in development, CMX-157.

Furthermore, your organisation is also investing in the reformulation of the existing tenofovir, with the goal of increasing bioavailability, hence reducing the required API and in turn the cost.

Other drugs in late-stage development such as the integrase inhibitor dolutegravir (50 mg once daily) also offer potential savings on manufacturing and could end up being cheaper than stavudine 20 mg by the time it would become available.

For the reasons outlined above, research and the resources it requires, as well as activist pressure should focus on increasing access to safer cost-saving alternatives to stavudine, not on seeking a comeback for a drug virtually abandoned in rich countries.

Yours sincerely,

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[12] FOSTER CITY, Calif., Nov 15, 2011 (BUSINESS WIRE). Gilead Sciences Finalizes Agreement with Tibotec Pharmaceuticals to Develop and Commercialize a Single-Tablet Regimen of Prezista(R) with Emtriva(R), GS 7340 and Cobicistat.