

AIDS Activism, Boehringer Ingelheim, and the Broken Social Contract

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Remarks at Boehringer Ingelheim Symposium

“HIV: From Yesterday to Tomorrow / HIV: da ieri in poi”

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[Note: This is a revised and expanded version of remarks I gave yesterday at the Boehringer Ingelheim symposium on HIV past and future. The two-day symposium is taking place at a business-style ‘hotel and resort’ called the Sheraton Golf Parco de’Medici some 20 minutes outside of Rome in a complex which includes conference facilities, a golf course, and sprawling mall-like commercial structures more typical of Las Vegas than of the Eternal City. The symposium includes an overview of the evolution of AIDS treatment with an emphasis on resistance to antiretroviral treatment and provides a venue for the introduction of Boehringer Ingelheim’s protease inhibitor, Aptivus[®] brand tipranavir.]

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Buon giorno.

First, I would like to apologize that the organizers of this symposium did not invite an Italian person living with AIDS or treatment activist to speak here.

Second, I thank the organizers for allowing me to give these remarks.

I am going to talk about AIDS activism and the broken social contract.

AIDS activism is a response to a global public health emergency.

It is a response to inequality and discrimination, and to the lack of human rights for women, men who have sex with men, injecting drug users, sex workers, prisoners, children, and others.

The United States, though among the richest countries in the world, has greater social and economic inequality than any other developed country. We spend 15% of our national product on health care, yet health outcomes are worse than those in many developing countries. In the US, infant mortality is higher than it is in Costa Rica. A person of color born in Harlem or the Bronx has a lower life expectancy than a person born in the Indian state of Kerala.

The economic inequalities in the United States are as great as those in some developing countries such as Brazil and South Africa, all three of them much richer than many countries stricken by AIDS.

The United States has more cases of HIV than any other developed country.

Over 1.2 million people in the US are living with HIV. Over 600,000 have died of AIDS. In New York City, where I live, 80,000 people have died of AIDS.

AIDS activism began when the epidemic first appeared in the gay communities of New York and San Francisco in the early 1980s. Now it is a worldwide movement for human rights, public health, high-quality and free medical care, and social justice.

AIDS activism built on a foundation of organizations formed by and for people with AIDS. Activists conducted demonstrations and direct action to build public awareness and political support and to mobilize resources to respond to the epidemic by creating legal protections, social programs, HIV prevention, health care, medical research, treatment access, lower drug prices, and informed and educated communities.

People with AIDS and activists were too weak to change the social inequalities in the US which denied rights to gay people, women, racial and ethnic minorities, drug users, prisoners, and others. But we were able to develop the skills and abilities to contribute meaningfully to medical research, and to mobilize public support to create strong AIDS research programs funded by the Federal government.

Treatment activism builds on a series of targeted campaigns to transform medical research, speed access to and approval of treatments to treat HIV and its opportunistic infections, subsidize access to medical care for people living with HIV/AIDS, and increase support for AIDS care and treatment in developing countries.

In 1988, activists demonstrated at the US Food & Drug Administration (FDA) for access to experimental treatments and for faster approval of new drugs for AIDS. In 1990, we demonstrated at the National Institutes of Health to demand full participation in the clinical trials networks which carried out studies of new treatments.

Activists demanded to participate in the design of clinical trials directed by the National Institutes of Health and pharmaceutical companies. Inspired by the activists' example, breast-cancer patient-advocacy groups made similar requests. The AIDS groups interrupted meetings and staged "die-ins" at the NIH, and, eventually, the physicians in charge of planning the clinical trials agreed to their demands. Laypeople now routinely sit on committees at the NIH, and on hospital's institutional review boards, which assess the ethicality and scientific merit of clinical trials, particularly those involving experimental drugs or procedures. (1)

By 1992, the FDA had codified new regulations for accelerated approval for new drugs to treat AIDS and other life-threatening diseases, by allowing drugs to be approved based on beneficial changes in surrogate markers, such as CD4 cell counts or later viral load levels, which were thought to predict clinical benefit.

By reducing the time it took to develop new drugs, and thus making it less expensive to invest in AIDS research, these changes drew more companies into developing treatments for HIV.

But activists also realized that the discoveries which led to new drugs and drug classes came from fundamental basic research on the biology of HIV and its interaction with the human immune system. Activists therefore fought to increase support for basic research on HIV/AIDS and to strengthen the planning, coordination, and evaluation of AIDS research at the National Institutes of Health (NIH) by creating a strong Office of AIDS Research (OAR) with the ability to draw on the advice and input of external scientists, with community involvement, in developing a comprehensive strategic plan for AIDS research, linked with the annual budget, to address the highest scientific priorities, fill gaps in research, and develop innovative approaches.

Activists succeeded in securing major increases in funding for AIDS research by the NIH. Last year NIH spent \$2.9 billion on AIDS research.

By 1996, the combination of political pressure, increased basic science, a more flexible regulatory requirement, greater industry involvement, and accelerated approval led to the approval of protease inhibitors and the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, the introduction of highly accurate viral load tests to assess the prognosis for progression of HIV to AIDS and to directly measure the impact of ART on HIV levels, and thus to the advent of highly active antiretroviral therapy (HAART)..

Within two years, the death rate from AIDS in developed countries – including the United States – dropped by over 2/3 due to the extraordinarily rapid introduction, dissemination, and uptake of HAART and viral load testing. The US death rate dropped from over 50,000 per year to about 16,000, where it remains today. In some countries with universal health care, mortality dropped even more.

But inequalities in the US health care system have persisted and worsened. Millions more Americans lack health insurance than even ten years ago. Huge corporations like General Motors are desperately shedding workers, shredding benefits, canceling pensions, and slashing health coverage. Hundreds of people with HIV who need therapy in the US are on waiting lists in states which do not adequately support their AIDS Drug Assistance Programs. Recent changes in Federal programs such as Medicaid and Medicare have made access to treatment more difficult for some. The Medicare drug benefit law actually prohibits the US government from negotiating lower drug prices with industry. This makes a travesty of the free-market system. In a truly free market, buyers and sellers each have access to accurate information about prices, quality, and alternatives. There is little or no access to information about what prices each company provides to different health care providers for different drugs. Oftentimes industry fails to meet its post-marketing commitments, and so it is not always clear which therapeutic alternative is best. Health insurance companies spend billions on administration, marketing, and cost shifting rather than on providing care. Poor people routinely go without needed diagnostics, drugs, care, and treatment because they are treated poorly in our fragmented health care system.

It is difficult for people in European countries with national health care systems to understand the deeply unjust, inequitable, and discriminatory health care system in the United States. But, conversely, European countries are not adequately funding the science base which leads to new treatments. Europeans must make larger contributions to medical research and international treatment access than they currently do. European countries do not spend as much as the US on publicly funded basic and applied research. This means, despite the accessibility of health care in most European countries, that drug companies have an even more disproportionate effect on medical research, since there is inadequate publicly funded biomedical research. Researchers and clinicians depend on industry for funding, information, and gratuitously lavish

junkets just as much or even more than they do in the United States. This week's Boehringer Ingelheim symposium, a thinly disguised promotional tipranavir jamboree, made this abundantly clear. But more on that in a moment.

Now I am going to first briefly sketch the changes which have occurred in global treatment access as a result of treatment activism around the world. Community-based political activism has created momentum for significant scale-up of ART access in a number of countries around the world, including major advances in Brazil, South Africa, Thailand, Uganda, Ukraine, and other countries.

Where community mobilization for ART access in developing countries has taken place, it has been due to strong civil society linked in many cases with democracy movements. Brazil, South Africa, and Thailand all moved towards democracy in the 1990s after decades of dictatorship. AIDS activists in those countries used the new structures of democratic accountability to demand access to ART. Even in countries which are not fully democratic, such as Uganda, strong civil society mobilization has made remarkable changes.

Brazil was the first developing country to adopt a policy of universal access to ART, in the mid-90s, and expanding to cover 87,500 people living with HIV by 2000 (2), when the Brazilian government began to promote its universal access program at international fora such as the International AIDS Conference at Durban in June 2000.

Influenced by the massive mobilization of South Africa's Treatment Action Campaign, the controversy over President Mbeki's denialist views about the HIV/AIDS link, and South African judge Edwin Cameron's dramatic opening speech calling for international distributive justice and a right to ART care for all, Durban marked the point at which the international consensus began to shift in favor of global treatment access. Soon after, generic companies began manufacturing ARVs at greatly reduced prices and making them available to individuals or countries who could pay. Drug prices for some first-line combinations came down from \$10,000 per year to less than \$300.

In 2002 the Global Fund to Fight AIDS, Tuberculosis, and Malaria was established. In 2003, the US announced the President's Emergency Plan for AIDS Relief (PEPFAR), and the World Health Organization (WHO) announced the target of supporting developing countries to treat three million HIV infected people by the end of 2005.

By the end of December 2005, according to the latest update from WHO, 1.3 million people in developing countries were receiving ART (3). While this is just 12% of the global need, it also represents a three-fold increase in ART access in just two years. In sub-Saharan Africa, the increase was eight-fold (800%). Yet the road ahead is far from clear. Without new contributions, the Global Fund cannot fund new or continuing programs past the current round. It is unclear whether the ongoing, UNAIDS/G8 led initiative to promote universal access to HIV/AIDS prevention, treatment, care, and support by 2010 has a chance of succeeding in mobilizing the resources necessary to build health systems capable of delivering life-long chronic care in the developing world.

The Role of Industry in AIDS Drug Development and the Broken Social Contract

It would be inappropriate for an activist speaking at a drug company symposium not to address the role of industry in research, treatment, access, and scale-up towards universal access. Since this symposium is sponsored by Boehringer Ingelheim I will address the role that company has played and should play in

AIDS treatment research and access initiatives.

First, I should make it clear that I believe the R&D based pharmaceutical industry has an indispensable role to play in discovering and developing diagnostics, drugs, and vaccines to improve human health. I mentioned above that industry plays a vital role in taking the discoveries made in fundamental research supported by public agencies such as the NIH and taking them to develop lead compounds and to bring new drug compounds and classes to market. A classic example of this process is the NIH-funded discovery in 1995-96 of the role of CCR5 and CXCR4 as HIV coreceptors and the role of industry in taking this basic science breakthrough and developing lead compounds and candidate drugs and testing them pre-clinically and in humans. Thus basic science advances ten years ago led to the ongoing clinical trials of drugs such as the CXCR4 inhibitor from Anormed (AMD-070) and the CCR5 inhibitors from Pfizer (maraviroc) and Schering (viroviroc). Whether they will actually work is still an open question.

Second, I believe that pharmaceutical companies are entitled to make a reasonable return on investment. If they do not make a profit they will not be able to stay in business. But drug companies must be part of a larger social contract to ensure that all people who need the benefits of new therapies receive them, regardless of whether they live in rich or poor countries or which kind of health system they have access to. And currently the drug companies are part of the broken social contract, rather than part of the solution.

Third, in spite of the detailed criticism which follows, I believe that Boehringer Ingelheim has made important contributions to HIV treatment, has the potential to make further discoveries, and can improve its performance by designing more informative clinical trials, responding more rapidly and effectively to scientific and community concerns, and assuring access to all who will need its therapies.

Boehringer Ingelheim and the Privileges of Privately-Held Pharmaceuticals

Boehringer Ingelheim developed and brought to market the first non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine (Viramune[®]), approved by FDA in 1996, and the tenth protease inhibitor tipranavir (Aptivus[®]), approved by FDA in summer 2006.

Boehringer Ingelheim is a privately-held, family-owned global R&D pharmaceutical company with its headquarters in Germany. According to a company press release (4) quoted in yesterday's *Financial Times* (5), last year,

Net sales grew by 17% to 9.5 billion euros (2004: EUR 8.2 billion). Operating income, comparable to EBIT, was 40% higher at over 1.9 billion euros (1.4 billion). The number of employees worldwide rose by some 1,900 to total 37,400 (+5.3%). Dr Alessandro Banchi, Chairman of the Board of Managing Directors, with responsibility for Pharma Marketing and Sales, said the financial year 2005 was clear confirmation 'that Boehringer Ingelheim has entered the group of leading international pharmaceutical companies, not only in terms of sales growth, but also in terms of profits'. 'We look back on a most satisfactory financial year,' Dr Banchi said... [BI] achieved an operating return (operating income in relation to net sales) of 20.2%, which Professor Marbod Muff, responsible at Boehringer Ingelheim for the Corporate Board Divisions Finance and Human Resources, described as 'exceptionally good'...

According to figures from the market analysts IMS, which all pharmaceutical companies use, Boehringer Ingelheim was last year the fastest growing company among the major international pharmaceutical groups. Boehringer Ingelheim grew by 23% (sales in constant euros),

while the pharmaceutical market average could only add 6%. This growth dynamic was particularly marked in the USA, where Boehringer Ingelheim's 33% growth clearly outstripped the US market (+5%). The company, which for the sixth time in a row has grown faster than the pharmaceutical company average, has in the meantime secured a world market share of around 2%, ranking it as No.14 internationally. Dr Banchi expects distinctly faster than average pharmaceutical market growth again in 2006. 'We trust in our own strengths and are confident that we can extend our position further in our market segments,' the Chairman said. Simultaneously, Dr Banchi underlined that successful growth and good profits are no end in themselves, but are the 'preconditions for developing innovative medicines to benefit people'...

The highlight of the last year was the market launch of the AIDS drug Aptivus®, a novel protease inhibitor which offers additional treatment options for patients with multiple resistance to other HIV drugs...

For years, the company's biopharmaceutical production has here been particularly successful, with net sales last year growing by 40% to 550 million euros..." (4)

Clearly the unique advantages R&D based pharmaceutical companies have in the distorted and fragmented US health care system are yielding concrete benefits for BI, as its 4 April 2006 press release indicates:

The most important regions for Boehringer Ingelheim last year were once again both American continents with 4.6 billion euros net sales. Europe contributed 3.1 billion euros to sales and Triple A (Asia, Australasia, Africa) 1.9 billion euros... The good development of net sales led to markedly higher income after taxes. This amounted to 1.5 billion euros, corresponding to an increase of almost 70% compared to the previous year. However, this result contains only part of the overall tax burden. The position regarding the taxation of partnerships in Germany – and the family-owned company Boehringer Ingelheim is such a partnership – includes only the trade tax, but not the income tax also incurred. This has to be shown on the balance sheet as 'capital withdrawn', said Prof. Muff." (4)

In Germany, the families who own BI must, alas, pay income taxes on their profits. Perhaps they should relocate to the United States where the Bush administration derides such injustice to the rich and promotes an end to this allegedly unjust "double taxation." Since BI does not have to report to public shareholders, or comply with legal and regulatory requirements which apply to publicly-listed companies, it benefits from the current system without having to play by rules which affect publicly-traded companies.

Dr Banchi und Prof. Muff drew attention to Boehringer Ingelheim's peculiarity as a company independent of the capital market. 'We can plan really long term,' said Dr Banchi. 'The development of our business is characterised by stability and continuity.' This also has a decisive influence on our vibrant corporate culture.

For the future, the company presents a positive picture. The product pipeline contains a number of promising candidates in various therapeutic areas. In 2005, almost 1.4 billion euros was invested in Research & Development + Medicine. That is 10% higher than the previous year. However, due to the very positive development of net sales the R&D+M expenditure as a share of net sales in Prescription Medicines slightly declined to 18.2% (2004: 19.3 %).

Many of Boehringer Ingelheim's successful products will be patent-protected or will enjoy exclusivity for a significant number of years. New market launches and indication extensions are to come in 2006, including pramipexole (Sifrol®/Mirapex®) in the indication restless legs syndrome – RLS. For Dr Banchi the goals for 2006 are clearly defined: 'We will maintain our dynamic

growth in 2006 too.’ (4)

BI’s independence from capital markets and its ability to plan for the long-term may well benefit people suffering from restless legs syndrome.

Vagaries of Viramune® (Nevirapine)

BI played a critical role by keeping the development of nevirapine alive despite discouraging early results which demonstrated that when used as monotherapy nevirapine could promote the outgrowth of NVP-resistant HIV within one week (7) . Another set of studies from Harvard prematurely claimed victory in a series of papers marred by laboratory errors followed up by clinical trials which did not combine all three anti-HIV drugs – in this case AZT, ddI, and nevirapine – simultaneously in people without previous treatment experience. TAG wrote up this dismal story in our December 1993 report on *The Crisis in Clinical AIDS Research* (

new drugs – including The drug was almost dropped. Luckily, some inside and outside the company realized this potential Achilles heel – which had already emerged with the nucleoside analogue RTIs AZT, ddI, ddC, 3TC, and d4T – could be delayed or prevented by the simultaneous introduction of three ARVs to individuals who had not previously received antiretroviral therapy. BI’s INCAS study, presented at Vancouver in 1996, showed that HAART did not require a protease inhibitor, and could also include an NNRTI as the anchor drug (8).

Viramune® was approved in 1996, but sales were never as robust as for the more potent protease inhibitors. Nonetheless the drug achieved a niche; by 2002, it was awkwardly wedged no. 8 between two forms of abavavir (Trizivir and Ziagen) in IMS health’s list of the top ten U.S. antiretrovirals by sales (9):

2002 Top 10 HIV Antiviral (J5C) Products By Global Sales*, 12 months ending

Rank	Product	Description**	Date of 1st Launch	Corporation
1	Combivir	NRTI	October 1997	GlaxoSmithKline (GSK)
2	Viracept	PI	March 1997	Pfizer
3	Zerit	NRTI	August 1994	Bristol-Myers Squibb (BMS)
4	Sustiva	NNRTI	September 1998	BMS
5	Epivir	NRTI	November 1995	GSK
6	Kaletra	PI	September 2000	Abbott
7	Trizivir	NRTI	December 2000	GSK
8	Viramune	NNRTI	June 1996	Boehringer Ingelheim
9	Ziagen	PI	January 1999	GSK
10	Crixivan	PI	March 1996	Merck & Co.

Source: IMS Monthly MIDAS, 2002

* Retail pharmacy markets in the U.S., Canada, Germany, Italy, France, Spain, U.K., Brazil, Mexico, Argentina, Australia, New Zealand, Japan.

Perhaps more important from a global perspective, the NIH-sponsored HIVNET 012 study, completed in 1998, was the first study to show that single-dose nevirapine, administered during childbirth, could dramatically reduce the transmission of HIV from mother to child (10). While previously ACTG 076 showed that twelve weeks of AZT had greater effects, single-dose NVP obviously had greater public health

implications for prevention of mother-to-child transmission (PMTCT) in resource-poor settings, and indeed it provided the first impetus for previously treatment averse United Nations agencies such as UNAIDS and UNICEF to begin sluggishly advocating for a more treatment-oriented approach to AIDS in poor countries.

While HIVNET 012, conducted in Uganda by NIH and without full regulatory support from BI to meet standards for FDA approval, had some deficiencies with respect to record-keeping and other administrative matters, numerous scientific reviews and rigorous retrospective analyses, as well as other controlled studies, have demonstrated that the underlying scientific conclusion is correct (11).

By Durban in mid-2000, activism to demand nevirapine access for pregnant HIV-positive women was a core demand for South Africa's Treatment Action Campaign (TAC) (12). Perhaps it was just a coincidence then – or more likely the presence of the global media and AIDS research elite – that elicited BI's announcement on 7 July 2000 of a five year free nevirapine donation program for PMTCT in developing countries (13). The program generated oceans of good publicity for BI, while actual supplies of free nevirapine slowly trickled to poor countries, hampered by logistical difficulties at every turn.

In addition the findings of the early Richman study of rapid development of resistance to nevirapine were followed by the evidence for the rapid emergence of resistance to even single-dose nevirapine. As James McIntyre told the 12th CROI in 2005, quoting Polly Clayden of UK's I-Base, "It's time to move on" from single-dose nevirapine (14).

Ultimately, despite the development of generic forms of nevirapine by many companies around the world, its price as the lowest of any generic NNRTI either as a single drug or in fixed-dose combinations (FDCs) (15), seven years of promises by BI, UNAIDS, UNICEF, and others, and massive increases in resources for HIV/AIDS prevention and care programs through GFATM, PEPFAR, and others, uptake of nevirapine for PMTCT remains pathetic. According to the 28 March 2006 WHO 3x5 update, "In most low- and middle-income countries ... less than 10% of pregnant women living with HIV/AIDS [are] estimated to be receiving antiretroviral prophylaxis. As a result, 1800 infants are infected with HIV every day..." (3, p. 36)

Clearly, while victory has a thousand parents, defeat is an orphan. It is not Boehringer Ingelheim's fault, or that of GFATM, PEPFAR, UNAIDS, UNICEF, or WHO that uptake of PMTCT is so pathetic – it is all of their responsibility, and that of governments that do not take care of their people. And it demonstrates the need for better infrastructure, human resources for health, robust supply chain management systems, and all the rest – but it is striking that eight years after its discovery, PMTCT appears to be progressing even more slowly than ART scale-up, which is much more complicated.

Meanwhile further complications of nevirapine when used as therapy (rather than in single dose PMTCT) emerged in 2004-2005. These concerns centered around sometimes-fatal hepatotoxicity associated with NVP, which had always been a known side-effect, but received renewed concerns after several women died in a clinical trial of emtricitabine (FTC) being conducted by Triangle (later bought by Gilead), which included AZT and nevirapine in both arms and was comparing FTC to its established cousin FTC.

The FDA asked Boehringer Ingelheim to conduct intensified reviews of the post-marketing database.

BI sponsored a special supplement on "Hepatic Safety and HAART" in the 2 March 2004 *Clinical Infectious Diseases*, and the title page noted, "This supplement is sponsored by Boehringer Ingelheim International." The editors of *CID* published an unusual disclaimer stating, "The

opinions expressed in this publication are those of the authors and are not attributable to the sponsors or to the publisher, editor, or editorial board of *Clinical Infectious Diseases*” (21) A lead article by guest editor Douglas Dieterich and colleagues reviewed cohort studies (rather than randomized trials or post-marketing FDA safety reporting. They stated:

HIV infected patients frequently present with elevated levels of serum transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]). This has often been attributed to the hepatic effects of antiretroviral (ARV) drugs, including nonnucleoside reverse-transcriptase inhibitors (NNRTIs). A review of cohort studies investigating the incidence of hepatotoxicity among patients receiving ARV therapy suggests that the overall rate of ALT and/or AST elevations is similar among all ARVs. (22)

This comparison looked at elevations in liver function tests (LFTs) rather than at the *severe, life-threatening hepatotoxicity* observed with NVP (but not with all other ARVs).

The rate of severe hepatotoxicity, ALT and/or AST levels >5 times the upper limit of normal (ULN), during therapy with NNRTIs is relatively low but may be significantly higher in patients with concurrent chronic viral hepatitis (hepatitis B or C). A comprehensive analysis of 17 randomized clinical trials of nevirapine demonstrated that 10% of all nevirapine-treated patients developed elevated levels of ALT and/or AST >5 times the ULN; however, almost two-thirds (6.3% of nevirapine-treated patients) of these elevations were asymptomatic. Symptomatic hepatic events were seen in 4.9% (3.2% 8.9%) of nevirapine-treated patients. (22)

The article leaves one with the impression that all ARVs have similar hepatic toxicity profiles at least when it comes to elevated LFTs. However, it did not look at comparative rates of severe, life-threatening, or fatal hepatotoxicity.

In the meantime, the FDA, after a post-marketing safety database review, required BI to change the Viramune package insert, which now begins with a prominent black box.

WARNING. Severe, life -threatening, and in some cases fatal hepatotoxicity, particularly in the first 18 weeks, has been reported in patients treated with VIRAMUNE®. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure. These events are often associated with rash. Female gender and higher CD4 counts at initiation of therapy place patients at increased risk; women with CD4 counts >250 cells/mm³, including pregnant women receiving VIRAMUNE in combination with other antiretrovirals for the treatment of HIV infection, are at the greatest risk. However, hepatotoxicity associated with VIRAMUNE use can occur in both genders, all CD4 counts and at any time during treatment. Patients with signs or symptoms of hepatitis, or with increased transaminases combined with rash or other systemic symptoms, must discontinue VIRAMUNE and seek medical evaluation immediately (see WARNINGS). Severe, life -threatening skin reactions, including fatal cases, have occurred in patients treated with VIRAMUNE. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions must discontinue VIRAMUNE and seek medical evaluation immediately (see WARNINGS). It is essential that patients be monitored intensively during the first 18 weeks of therapy with VIRAMUNE to detect potentially life-threatening

hepatotoxicity or skin reactions. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of these events. Do not restart VIRAMUNE following severe hepatic, skin or hypersensitivity reactions. In some cases, hepatic injury has progressed despite discontinuation of treatment. In addition, the 14-day lead-in period with VIRAMUNE 200 mg daily dosing must be strictly followed (see WARNINGS). (23)

The revised prescribing information was released on 11 January 2005, just nine months after the misleading coverage in the March 2004 *CID*, and was followed by an “FDA Public Health Advisory for Nevirapine (Viramune)” (24).

Unfortunately the politics of HIV denialism in South Africa and elsewhere seized on the newly clarified safety concerns – as they had previously on the unrelated issues regarding record-keeping in the HIVNET 012 study – to cast doubt on the underlying safety and efficacy of nevirapine for either PTMCT or on ART regimens.

Nonetheless BI’s support for the *CID* supplement and what some have suggested was its less than forthright response to safety considerations raised by FDA and others in the decade since the licensing of nevirapine clearly provide an opportunity for the company to reflect on its behavior and commit to addressing future safety concerns in a more pro-active, transparent fashion. This means taking an aggressive approach to studying the toxicities associated with their drugs in well-designed long-term safety studies, investigating the interactions between their drugs and other commonly used treatments, trying to understand the pathogenesis of hepatotoxicity, providing clinicians and patients with clear, accurate information about the detection and management of severe adverse events, and fulfilling their post-marketing commitments to FDA and other regulatory authorities.

In many places where nevirapine is now used as the most common anchor drug in first-line ART regimens in countries scaling up ART programs, lab and clinical capacity needs to be made available to monitor liver function tests (LFTs) when possible, and people on ART, providers, and the health system need to be trained and encouraged to be vigilant for clinical symptoms which may suggest NVP hepatotoxicity. Nothing is ever simple in HIV treatment.

More Complications – The Tortured Tipranavir Tale

Which brings us to tipranavir. Perhaps no approved antiretroviral has had a more tortuous development course. First introduced into the literature in 1997 as PNU 140690, tipranavir (TPV) was initially developed by Pharmacia & Upjohn, a company soon swallowed up in the wave of pharmaceutical mergers which dramatically slowed down development of a number of HIV drugs, the former PNU compound included.

After giving a talk on “the Making of an AIDS Activist” at the European Community Advisory Board (ECAB) in November 1998 – coincidentally held in Rome, albeit in more congenial activist surroundings – I attended the ECAB meeting with Pharmacia where TPV was first discussed. Pharmacia decided to leave HIV research before being swallowed up by Pfizer in 2002. TAG’s ARV pipeline report from 2002 lists two other P&U drugs as casualties of its decision to leave the field and two Parke-Davis compounds as casualties of the latter’s merger with Pfizer; these were just a few victims of the merger-mania massacre (17).

Tipranavir got a reprieve – just barely; in 2001, Boehringer Ingelheim decided to take up PNU 140690 for development; we reported on it after the Buenos Aires IAS conference in 2001:

Despite prophecies of imminent doom periodically uttered by paranoid activists-some of whom recently claimed that activist pressure to lower antiretroviral prices in developing countries was leading drug companies to flee the HIV field – the IAS conference reflected a rather healthy, if underwhelmingly inventive or innovative, drug pipeline... After a long hiatus, tipranavir has been transferred from Pharmacia & Upjohn, which left the HIV field, to Boehringer-Ingelheim (which passed on P&U's other antiretroviral, delavirdine). Tipranavir is structurally different from other protease inhibitors and hence exhibits activity against most PI-resistant HIV. On the downside, tipranavir has a daunting pill count.

The tipranavir data presented in Argentina were somewhat confusing, as the formulation changed mid-study. In addition, tipranavir was given in combination with low-dose ritonavir in order to boost the drug's less than overwhelming pharmacokinetics...

Boehringer held a spirited community meeting where they were questioned aggressively on these results, although some of the problems with the development plan were the legacy of the previous sponsor. For example, the dose-ranging study included efavirenz, which is likely to affect the drug's pharmacokinetics. Despite its intriguing resistance profile, the combination of high pill count, bizarre pharmacokinetics and significant toxicity poses a trinity of major obstacles for this drug. (18)

Over the subsequent years BI conducted two studies of tipranavir in highly treatment experienced patients, RESIST-1 and RESIST-2. The studies allowed participants to use T-20 (enfuvirtide) and generally those who added both TPV and T-20 to their regimen did better. However the results of the RESIST studies were difficult to interpret due to the complex nature of the patients and their HIV in the studies, because of early treatment switches, and other confounding variables. As Keith Alcorn reported in *AIDSMAP* after the FDA hearing,

The United States Food and Drug Administration's Antiviral Drugs Advisory Panel voted 11-3 in favour of accelerated approval for the new protease inhibitor tipranavir (Aptivus) after public hearings yesterday in Washington DC.

Tipranavir is being recommended for approval in protease inhibitor-experienced HIV-positive patients, although the final labelling and approval must be decided by the FDA by June 22nd. The panel voted to recommend a twice daily dose of 500mg of tipranavir boosted by 200mg of ritonavir, as studied in phase III trials of the drug.

Tipranavir has been studied in two large trials in patients with protease inhibitor resistance (RESIST 1 & 2 studies), which showed that the drug was more effective than other boosted protease inhibitors when combined with at least two other drugs chosen after resistance testing (an optimised background regimen).

Although the panel voted to approve tipranavir, they expressed caution and asked for further studies to be carried out to guide use of the drug.

In particular the FDA highlighted problems with potential drug interactions and liver toxicity. They noted that interaction studies looking at a wide range of cytochrome p450 enzymes and drugs metabolised through those pathways have not yet been carried out, despite the fact that tipranavir also inhibits CYP1A2, CYP2C9, CYP2C19 and CYP2D6. Grade 3 or 4 liver toxicity was noted in 10% of tipranavir treated patients, and emerged significantly more quickly in both RESIST studies. The same was true for triglyceride and cholesterol elevations.

A higher rate of rash was also seen in women than men treated with tipranavir in phase I and phase II trials, but no difference between the tipranavir group and the control group was seen in the RESIST studies. However the FDA says that the small number of women included in these studies makes it impossible to draw definitive conclusions.

“I clearly would urge the pharmaceutical sponsor, since we know that there is this persistent elevation in liver function studies, to generate data that lets us know the baggage with elevation over time,” committee member Lauren Wood (Uniformed Services University of Health Sciences) said. (25)

Thus, four years after the first BI meetings with the community on TPV, the “trinity of obstacles” noted in the September 2001 *TAGline* remained of concern, as Bob Huff recounted in his update from the fall 2005 Dublin satellite symposia:

Tipranavir (Aptivus) is a recently US-approved protease inhibitor that has been targeted for salvage therapy. Jurgen Rockstroh from Germany reviewed the results from the RESIST studies of tipranavir versus best available therapy in highly treatment-experienced individuals. At 24 weeks, 34% of patients in the tipranavir group had HIV RNA below 400 copies/mL compared to only 15% of those in the comparison group. Subsequently, during a scientific session at the conference, 48 week RESIST results were reported that continued this theme, with about 30% of the tipranavir group below 400 copies versus 13.8% in the comparison group. Clearly there is an advantage to having tipranavir on board, but these low numbers speak to the pressing need for overall improvements in salvage therapy. For patients who included Fuzeon in their regimens, the prospect of success was brighter, with 50% of those on tipranavir having a protocol-defined treatment response. This demonstrates the importance of including at least two active drugs when constructing a salvage regimen; if only one active drug is added to a failing regimen, then the benefit will likely be short lived.

Most dropouts in this study were due to viral failure in the comparison arm and were switched to tipranavir after 8 weeks, which necessarily limits any comparative safety data after that point. The selection of Jurgen Rockstroh, widely known as a hepatitis expert, to present the tipranavir data speaks to concerns about the drug's potential for liver toxicity. In the 24-week RESIST data, grade 3 or 4 ALT elevations were reported in 5.9% of those receiving tipranavir and in 1.8% of those in the comparison arm. Rockstroh acknowledged that the risk of liver toxicity is higher in patients receiving tipranavir, especially those with HBV or HCV coinfection. He recommends routine monitoring and discontinuation if elevated liver enzymes are accompanied by symptoms. Aside from this issue, Rockstroh said, the safety profile of tipranavir was comparable to other PIs used in RESIST.

David Back from the UK addressed one of the other difficulties with boosted tipranavir: how to use it in combination with other drugs. An early study of tipranavir in combination with several protease inhibitors revealed that it could dramatically lower the levels of saquinavir, amprenavir, and Kaletra, which effectively ruled it out for use in a dual boosted-PI strategy. Back, one of the world's experts in drug interactions walked through what else is known about how tipranavir interacts with others. There seems to be no relevant interaction between tipranavir and efavirenz or nevirapine or with the NRTIs, including tenofovir. Coadministration with the PIs, of course, is not recommended. There are also likely significant interactions with certain TB drugs, some statins, some antifungals, and probably other drugs. The bottom line is that the net effect of tipranavir is difficult to predict and clinicians should be mindful of other, unrecognized potential interactions. (19)

The FDA-approved labeling for Aptivus included a now-familiar black-box warning on tipranavir's hepatic side-effects:

APTIVUS co-administered with 200 mg ritonavir has been associated with reports of clinical hepatitis and hepatic decompensation including some fatalities. Extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C co-infection, as these patients have an increased risk of hepatotoxicity. (26)

FDA required BI to complete or conduct at least 18 post-marketing studies, including reporting the 48-week results of RESIST-1 and RESIST-2; studies in children and adolescents; drug-drug interactions studies of TPV/ritonavir twice daily and atazanavir, buprenorphine/naloxone, carbamazepine, tadalafil, ribavirin/pegylated IFN alpha 2a, methadone; carcinogenicity studies in mice and rats; long-term 48 week safety and efficacy of TPV/rtv in ARV native patients in study 1182.33 including drug resistance analyses from patients with virologic rebound and metabolic changes; a 48-week "prospective observational diversity cohort study with tipranavir/ritonavir twice daily stratified by race and gender in HIV-positive patients to assess efficacy and safety, including potential risk parameters such as CD4+ cell count; a "48-week prospective observational cohort study with tipranavir/ritonavir twice daily in patients co-infected with HIV and HBV or HCV to assess efficacy and safety. BI will discuss potential therapeutic drug monitoring substudy for this protocol with the FDA"; TPV/rtv pharmacokinetics in HIV-negative subjects with Child-Pugh B liver disease; a "CYP/P-gp mechanistic study to determine effect of tipranavir/ritonavir on individual CYPs"; and "a formal QT prolongation study" (27).

It is fortunate that FDA is requiring such detailed and extensive post-marketing studies under its accelerated approval authority; however, past experience shows that many companies do not fulfill their post-marketing commitments. A recent FDA study showed that 154 drug sponsors had 1,231 open postmarketing commitments. By 30 September 2005, two thirds (797, 65%) were still "pending", 231 (19%) "ongoing", 28 (2%) "delayed", 3 (<1%) "terminated, and just 172 (14%) "submitted" (29). This is a rather dismal performance by industry and reflects the need for stronger FDA authority to compel sponsors to fulfill their commitments, as well as the need for more robust post-marketing pharmacovigilance.

Hence, FDA and the community must be vigilant in ensuring that BI fulfills its promises here.

Thus, it is hard to know how useful TPV will really be in the clinic. With its plethora of side effects, serious liver toxicity, and bizarre pharmacokinetics, it may be reserved for individuals able to tolerate it and who need a stopgap protease inhibitor before the introduction of possibly more forgiving alternatives such as Tibotec's forthcoming protease inhibitor darunavir, or – still speculatively as they are in earlier phases of study – the Pfizer or Schering CCR5 inhibitors, the Gilead or Merck integrase inhibitors, or other potential new ARV candidates.

Perhaps fearing that its brief moment in the sun would quickly be eclipsed by these rapidly advancing alternatives, BI decided to price Aptivus at a record \$13,410 per year wholesale in the United States, the highest price for any protease inhibitor. This certainly betrayed, at the very least, a dismaying indifference to the plight of U.S. HIV-infected people who might fall between the cracks in the fragmented health system, or even a more cynical urge to gorge on excess profits as quickly as possible due to fears of a vanishingly small window of opportunity to obtain market space.

The AIDS Treatment Activists Coalition (ATAC) responded to BI's unprecedented pricing move with a public warning that drug companies were engaging in a "steady onslaught of unreasonable, unacceptable, and unjustified" increases in the prices of therapies to treat HIV... 'Sadly, Boehringer-Ingelheim failed to realize that the size of the potential Aptivus market is directly tied to patients' access through publicly funded programs, and they just made that market a lot smaller,' said Lei Chou," a respected HIV community expert on drug pricing and reimbursement in the US (27).

On 23 February 2006, BI held a conference call with US treatment activists to announce that it was dropping the 500/200 mg tipranavir/ritonavir arm from the ongoing 1182.33 study in ARV naives which was comparing two doses of TPV/rtv (500/200 and 500/100) to Kaletra. "Following a thorough review of the 48-week data in this study, and with the recommendation of the DSMB, Boehringer Ingelheim has decided to close the Aptivus /ritonavir 500 mg/200 mg study arm. Safety in treatment-naïve patients in both Aptivus /ritonavir study arms was generally similar to the comparator lopinavir/ritonavir arm. However, the rate of asymptomatic liver enzyme elevations reported in the Aptivus /ritonavir 500 mg/200 mg study arm was higher than in the other study arms and thus presented a less favorable benefit-risk profile for these treatment-naïve patients." (30) BI refused to disclose the number of events which occurred, the relative risks between study arms, or to describe in any detail the reasons other than what they stated in their press release, saying fuller disclosure had to wait until an unspecified future scientific conference. This continuing evasive behavior stood in stark contrast to Pfizer's detailed disclosure regarding a single, severe adverse event in its ongoing maraviroc study in ARV naïve individuals. The fact that the dose combination which is FDA approved for use in treatment experienced individuals was now deemed too toxic for treatment naïve ones indicates the alarming degree to which BI has failed to clearly define a dose which is both safe and effective for use in diverse HIV infected individuals.

In conclusion, Boehringer Ingelheim has failed to live up to the best practices which should be expected for the world's fifteenth-largest R&D based pharmaceutical company. In its interactions with treatment activists in the US or Europe, BI clings behind the excuses of being small, family owned, and privately held, to justify its small studies, inadequate research into side effects or resistance, and failure to fulfill post-marketing study commitments. Similarly, when activists or from developing countries or NGOs such as MSF implementing ART and PMTCT programs in developing countries complain about difficulties accessing BI, obtaining regulatory information, or obtaining promised discounted or free drug donation programs, BI claims that it lacks the capacity to respond to the myriad of requests coming from places where it is understaffed or relies on intermediates. Yet at the same time, in its annual reports to investor, BI trumpets its unparalleled growth, intention to join the big leagues, commitment to groundbreaking innovative research, and brags that being privately-held enables it to plan long-term, while simultaneously complaining its profits are doubly-taxed in Germany.

BI needs to decide which role it intends to play. If it really wants to be a global player, it must be more accountable, transparent, scientifically rigorous and respectable, and let community activist networks have access to the most timely and accurate scientific information. It must make its products accessible to all who need them without pricing entire countries or populations out of its markets. It must meet and exceed its commitments to FDA. It must conduct solid research into the reasons for drug toxicities and how to manage them in diverse population groups affected by HIV, HBV, HCV, drug substitution therapy, and other combinations.

Conclusion

I have discussed the need for stronger public investment in biomedical research to make the discoveries which will lead to better diagnostics, drugs, and vaccines for deadly diseases. In the US, the NIH is facing flat funding. In Europe, 40% of the EU budget is devoted to agricultural subsidies which impoverish farmers and countries in the developing world while diverting resources from education, R&D, and creation of jobs for the unemployed. Both US and the EU need to invest more in public research.

The social contract between drug companies and the public sector is broken, especially in the US. While companies make their greatest profits in the US, they deny public information about pricing schemes, extract maximum short-term profits, while failing to address the need for universal health care in the world's richest country.

Companies are not meeting their post-marketing commitments to find out how best to use drugs licensed under accelerated approval mechanisms for which AIDS activists fought and without which many people with AIDS would have died. But accelerated approval demands that industry continue rigorously studying their drugs after approval, and in this many companies – BI among them – have failed woefully.

Companies also need to contribute more effectively to the global movement for universal access to ARV treatment by the year 2010. Instead of seeking to file pre-emptive patent applications in all poor and middle-income countries, they should explore innovative ways of making their products more widely available, including the use of voluntary licenses to generic manufacturers, assisting the latter in regulatory filings, working with GFATM, PEPFAR, UNAIDS, UNICEF, WHO, the World Bank, and other funding and technical partners to maximize available treatment resources without bankrupting the system or diverting funds needed to strengthen health systems in developing countries into the pockets of wealthy families in rich countries.

Companies need to commit to rapid and full disclosure of emerging safety concerns and conduct follow-up studies to elucidate the causes and define the management of adverse events.

We need a global movement for universal access to public health, free medical care, human rights, and social justice.

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Postscript. After my talk, BI corporate spokeswoman Judith von Gordon-Weichelt approached me to clarify that BI's 2005 global sales, not profits, were \$10 billion. She stated that as she was in public relations we were engaged in the same kind of work. I told her that I was an activist working for social change while she was a well-paid employee of a wealthy private German drug company whose job was to ensure that bad publicity was deflected rather than to frankly address critical issues that needed to be resolved. She stated that it was not accurate that Aptivus would soon be eclipsed by other newer ARVs and I asked if she could provide me with sales figures on tipranavir. She demurred. Another person told me that as patients did not pay directly for drugs in Europe the price did not matter here. I went back to my hotel room to revise and expand my remarks. Later that night, the Italian physicians were taken by bus to an opulent mansion overlooking Rome for champagne and a three-course dinner. I sat with some Italian activists and we discussed the shoddy methodology and confusing results of the RESIST studies. Stacks of Alan Bennett's *La Ceremonia del Massaggio* (*The Laying on of Hands*) were piled up at the exits so that

everyone could have a free (albeit literary) massage after dinner. The sated diners returned to their golf-course hotel and resort after dinner. To top it all off, upon return to the hotel room, participants were welcomed by a small gift-wrapped box with a small silver bowl, “set made of silver ‘800 with hand-engraved border.” (31)

In the early 1990s, the political system which had dominated Italy since World War II collapsed in a wave of corruption scandals known as “Tangentopoli.” According to Wikipedia,

Tangentopoli (Italian for bribeville) was the name used to indicate the corruption-based system that dominated Italy until the Mani pulite [clean hands] investigation delivered it a deadly blow in 1992. Whether things have really changed since then, or whether only the names of those involved have, is a matter of debate.(32)

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