ACCELERATED APPROVAL AND POST-MARKETING COMMITMENTS: A DELICATE BALANCE

Tracy Swan, Lei Chou. Treatment Action Group, New York, NY

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"Access to promising new drugs is a right one cannot deny patients with a fatal illness. However, this right carries with it the responsibility to provide information that will advance science and help future generations of patients."

Carlton Hogan 1961-2003[1]

BACKGROUND

AIDS activists have focused on HIV drug development for more than two decades. In 1992, in part due to pressure from AIDS activists and pharmaceutical deregulators, FDA instituted Accelerated Approval regulations, allowing earlier approval of drugs for serious, or life-threatening diseases, based on unmet need and a surrogate endpoint. Clinical benefit and questions about optimal use are determined in subsequent trials, known as post-marketing commitments (PMCs).

AIDS activists welcomed accelerated approval, but pressed for collection of data on pharmacokinetics, drug-drug interactions, dosing, efficacy and toxicity by disease stage, and in specific populations, during registration trials. They argued that post-marketing commitments are not always required or conducted expeditiously. Often, PMC results are not available until drugs have already been on the market for years.

Valid scientific rationale, justice (as outlined by the Office of Human Subjects Research's 1974 Belmont Report), and HIV demographics in the United States argue for adequate enrollment of women, people of color, and current and former injection drug users, many coinfected with viral hepatitis, in registration trials[2].

Updated demographic data on HIV prevalence in the US indicate that women constitute ~25% of cases, African Americans a staggering 46%, Hispanics ~17%, and injection drug users ~18%[3].

METHOD

FDA databases, MedWatch reports, antiretroviral product labeling, and medical literature were reviewed. Instances when emergent safety and toxicity issues would have warranted studies in, or greater inclusion of, specific populations in clinical trials of novel antiretroviral agents were identified, the nature and status of post-marketing commitments were characterized, and the extent of pediatric labeling was assessed.

Under-Enrollment of Women In HIV Clinical Trials: A Tragic Example

"An observed lower incidence of hepatotoxicity in previously reported trials of nevirapine may be explained by the limited number of women studied...[4]"

Inadequate enrollment of women in HIV clinical trials has been a chronic—and sometimes dangerous—problem. Nevirapine presents an example of consequences of underenrollment of women in clinical trials. Liver toxicity, ranging from mild to life threatening, is a known adverse event associated with nevirapine use. In 2003, Stern and colleagues at Boehringer Ingleheim reported that:

"No consistent CD4 cell count cutoff could be identified in women that was associated with an increased risk of ALT/AST elevations…Use of nevirapine was not associated with a significantly increased risk of clinical hepatotoxic events, including liver failure or liver related death, compared to therapy with other antiretroviral drugs[5]."

The hepatotoxicity risk among women was not fully characterized until almost a decade after the drug was approved. Women with a CD4 count of <250 cells/mL were identified as the population at highest risk for serious, nevirapine-associated liver toxicity in a 2005 FDA Public Health Advisory, which clearly spelled out risks:

"Females and patients with higher CD4+ cell counts are at increased risk of liver toxicity. Females have a three fold higher risk of symptomatic nevirapine liver toxicity than males, and females with CD4+ cell counts > 250 cells/mm^3 have a 12 fold higher risk of symptomatic liver toxicity than females with CD4+ cell counts < 250 (11% vs. 0.9%)[6]."

People who are coinfected with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) constitute ~35% of all HIV-positive people in the United States[7,8]. Yet they have been virtually excluded from, or underenrolled in, many clinical trials due to liver enzyme elevations (at times without a compelling rationale for this criteria). There has also been a failure to perform drug-drug interaction studies on methadone and buprenorphine. Thus, an opportunity to pick up early signals of differing pharmacokinetics and/or toxicity in this population is lost. Characterization of potential antiretroviral hepatotoxicity among coinfected people should occur in clinical trials, where monitoring for side effects, adverse events and laboratory abnormalities is particularly vigilant, rather than during widespread use after approval.

Genetic polymorphisms can have an impact on exposure, toxicity, response and hypersensitivity to antiretroviral agents. Pharmacogenomic analysis is likely to become a mainstay of medical practice in the future. Racial differences in the distribution of genetic polymorphisms argues for diverse enrollment in clinical trials. For example, a genetic polymorphism in cytochrome CYP2B6, called TT, is associated with higher efavirenz levels. The TT polymorphism is more common in persons of African descent (versus people of European or Asian descent). Studies have reported that people with the TT polymorphism are more likely to have higher efavirenz levels, more central nervous system side effects, and are more likely to discontinue efavirenz[9-11].

Inadequate Representation and Recent FDA Requests for PMCs

The insufficient enrollment of special populations—an umbrella term for women, people of color, and people with common comorbid conditions, such as renal impairment and viral hepatitis—has led FDA to request PMCs for five recently-approved antiretroviral agents.

Populations in Preapproval Studies and Post-Marketing Commitments, 2005-2008

Aptivus (*tipranavir*) Approved on June 22, 2005

Women	12%
HBV/HCV Coinfection	~10%
Renal/hepatic Impairment	Has not been studied in moderate or severe hepatic impairment or severe hepatic impairment Renal clearance is negligible, therefore difference in clearance not expected or studied in persons with renal impairment
PMC	Released from: methadone/buprenorphine interaction study; 48 week prospective observational diversity cohort study stratified by race and gender to assess efficacy and safety including potential risk parameters such as CD4 count & coinfection Pending: drug-drug interaction study of PEG-IFN alfa 2a and TPV/rtv; PK in HIV-negative persons with Child Pugh B liver disease; formal QT prolongation study

Intelence (*etravirine*) Approved on January 18 2008

Women	~10%
HBV/HCV Coinfection	12.4%
Renal/hepatic Impairment	Studied in mild and moderate hepatic impairment Renal clearance is negligible, therefore difference in clearance not expected or studied in persons with renal impairment
PMC	48 week study of TX experienced females to elucidate any potential differences in safety and efficacy

Isentress (*raltegravir*) Approved on October 12, 2007

Women	TX Experienced: ~12%; TX Naïve: 20%
HBV/HCV Coinfection	TX Experienced: HBV coinfected 6%; HCV coinfected ~9%; HBV/HCV <1%. TX Naïve: 7% overall
Renal/hepatic Impairment	Studied in moderate hepatic impairment and severe renal impairment
PMC	48 week non randomized open label single arm study in 200 people at least 50% African American and at least 25% female to characterize efficacy and safety in raltegravir in a population that closely reflects the U.S. HIV-1 infected patient population

Prezista (*darunavir*) Approved on June 23, 2006

Women	TX Experienced: ~11%; TX Naïve: 30%
HBV/HCV Coinfection	TX Experienced: Yes, number unspecified; TX Naïve: ~13%
Renal/hepatic Impairment	Not studied in people with hepatic impairment Studied in people with moderate renal impairment
PMC	Conduct a study of darunavir/r in TX experienced female patients to elucidate any potential gender differences in efficacy and safety; drug-drug interaction study with buprenorphine/nalaxone

Selzentry (*maraviroc*) Approved on August 6, 2007

Women	TX Experienced: ~11%; TX Naïve: 29%
HBV/HCV Coinfection	TX Experienced: HBV coinfected 6%; HCV coinfected 6% ; TX Naïve: unknown
Renal/hepatic Impairment	Not specifically studied in renal impairment or sufficiently studied in hepatic impairment
PMC	Study in coinfected people including people with Child-Pugh class C; asses effect of renal impairment on marivaric PK at a dose of 150 mg combined with a boosted protease inhibitor (mild, moderate renal impairment) and 300 mg alone in people with severe renal impairment and on dialysis

Sources:

Aptivus (Boehringer Ingelheim) (tipranavir) label.
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Intelence (Tibotec) (etravirine) label.
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Saag M, Ive P, Heera J, et al. (Abstract WESS104) A multicenter, randomized, double-blind, comparative trial of a novel CCR5 antagonist, maraviroc versus efavirenz, both in combination with Combivir (zidovudine [ZDV]/lamivudine [3TC]), for the treatment of antiretroviral naive patients infected with R5 HIV 1: Week 48 results of the MERIT study.

Program and abstracts of the 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention; July 22-25, 2007; Sydney, Australia.

Steigbigel RT, Cooper DA, Kumar PN, et al; BENCHMRK Study Teams. Raltegravir with optimized background therapy for resistant HIV-1 infection. N Engl J Med. 2008 Jul 24;359(4):339-54.

Children Have Been Consistently Overlooked in HIV Drug Development

Worldwide, there are two million HIV-positive children; in 2007, ~370,000 children under 15 years of age were infected, the majority through mother-to-child transmission[12]. Although the 2003 Pediatric Research Equity Act (PREA) requires studies of drugs and biologic agents likely to be used in children, these often lag far behind target completion dates because they can be deferred when drugs are ready for adult approval prior to completion of pediatric studies.

Antiretroviral Agents That Do Not Have Pediatric Labeling

Nucleoside/tide Reverse Transcriptase Inhibitors

Epzicom (*abacavir/lamivudine*) GlaxoSmithKline. Approved on August 2, 2004
Safety and efficacy in pediatric patients not established;
contraindicated in children <12 yr. due to fixed dosage form that cannot be adjusted

Trizivir (*abacavir, epivir, zidovudine*) GlaxoSmithKline. Approved on November 15, 2000
Safety and efficacy not established in pediatric patients, and should not be administered to adolescents weighing <40 kg

Truvada (*tenofovir/emtricitabine*) Gilead Sciences. Approved on August 5, 2004
Safety and efficacy not established in pediatric patients <18 years

Viread (*tenofovir*) Gilead Sciences. Approved on October 26, 2001
Safety and efficacy not established in pediatric patients <18 years

Non-nucleoside Reverse Transcriptase Inhibitors

Intelence (*etravirine*) Tibotec. Approved on January 18, 2008
Safety and efficacy in pediatric patients not established

Protease Inhibitors

Aptivus (*tipranavir*) Boehringer Ingleheim. Approved on June 22, 2005
Safety and efficacy in pediatric patients not established

Invirase/Fortovase (*saquinavir*) Hoffman-La Roche. Approved on December 6, 1995
Fortovase on November 7, 1997, New formation approved December 17,2004
Safety and efficacy in pediatric patients not established

Prezista (*darunavir*) Tibotec. Approved on June 23, 2006
Safety and efficacy in pediatric patients not established

Reyataz (*atazanavir*) Bristol Myers Squibb. Approved on June 20, 2003
Safety and efficacy in pediatric patients not established

Entry Inhibitors

Selzentry (*maraviroc*) Pfizer. Approved on August 6, 2007
Safety and efficacy in pediatric patients not established

Integrase Inhibitors

Isentress (*raltegravir*) Merck. Approved on October 12, 2007
Safety and efficacy in pediatric patients not established

Sources:
Food and Drug Administration. Drugs Used in the Treatment of Pediatric HIV Infection (current as of December 2007).
Available on-line at: http://www.fda.gov/oashi/aids/pedlbl.html (accessed November 11, 2008)

Food and Drug Administration. HIV/AIDS Historical Time Line.
Available on-line at: http://www.fda.gov/oashi/AIDS/miles.html (accessed November 17,2008)

Intelence Full Prescribing Information,
available on-line at: http://www.intelence-info.com/intelence/full-prescribing-info.html (accessed on November 17, 2008)

PMCs allow access to medications while important clinical questions are addressed. Unfortunately, initiation and completion of PMCs may lag for years. According to the FDA Summary of Information From Postmarketing Study Progress Reports, there were 1,281 open PMCs as of September 2007; only 14% were ongoing. FDA's post-marketing database was reviewed for examples of tardy antiretroviral PMCs.

Outstanding Post-Marketing Commitments

Aptivus (*tipranavir*) Boehringer Ingleheim. Approved on June 22, 2005

PMC	Due Date	Status
Drug-drug interaction study of PEG-IFN alfa 2a and TPV/rtv	6/30/2007	PENDING*
PK in HIV negative persons with Child Pugh B liver disease	12/31/2007	PENDING
Formal QT prolongation study	6/30/2006	PENDING

Epzicom (*abacavir/lamivudine*) GlaxoSmithKline. Approved on August 2, 2004

Prepare and submit summary of GSK's cumulative research on possible genetic correlates of hypersensitivity to abacavir	5/31/06	PENDING

Prezista (*darunavir*) Tibotec. Approved June 23, 2006

Drug-drug interaction study of buprenorphine/nalaxone	1/31/2008	DELAYED** Not yet verified

Trizivir (*abacavir, epivir, zidovudine*) GlaxoSmithKline. Approved on November 15, 2000

Provide data on geno/phenotypes of baseline and on-therapy isolates from patients receiving trizivir w/o other ART. Data from study CNA3005 (96 weeks) will be provided in a virology report with data in the HIV resistance template	8/31/2005	PENDING

Truvada (*tenofovir/emtricitabine*) Gilead Sciences. Approved on August 5, 2004

Use of Truvada in people with significant renal impairment (CrCl <30 mL/min)	11/30/2005	PENDING
Data on 48 W safety efficacy and resistance from completed studies GS 03 934 and ABT M02-418	8/02/2006	PENDING

Ziagen (*abacavir*) GlaxoSmithKline. Approved on December 18, 1998

Data on use in adolescent patients in PACTG 1018	4/15/05	PENDING
Provide information on status and outcome of ACTG 321 (evaluate abacavir in neonates)	4/15/05	PENDING
Submit HIV-1 viral resistance and cross-resistance data for ABC in the agency requested format for the agreed completed studies along w/revised labeling	6/15/2004	PENDING
Provide data on the in vitro susceptibility of NNRTI resistant HIV-1 isolates to abacavir and data on the in vitro susceptibility of abacavir-resistant HIV-1 isolates to approved NNRTIs to the FDA	10/15/2005	PENDING
Conduct and submit meta-analysis of data from ABC clinical trials to assess the rate of psychiatric events (including depression, worsening depression, suicidal ideation/events and acute psychosis) on ABC versus control arms	10/15/2005	PENDING

*PENDING: The study has not been initiated, no subjects have been enrolled or animals dosed.
**DELAYED: The original projected date for initiation of patient accrual or animal dosing has not passed.

CONCLUSION

Delaying clinical development and approval of antiretroviral agents is not beneficial to anyone, but the failure to characterize population-specific adverse events, differences in drug metabolism, and drug-drug interactions until years after drugs are marketed calls for action. People living with HIV and their medical providers deserve more information to inform safe and effective treatment choices.

Pre-approval trials must enroll more women, people of color and people with prevalent comorbid conditions to characterize adverse events in these groups as early as possible. Pharmacokinetic studies in persons with renal and hepatic impairment should be conducted prior to approval unless there are compelling safety reasons to avoid performing them. Drug-drug interaction studies with other antiretroviral agents, hormonal contraceptives, opiate substitution therapy, and other commonly used medications should be performed as soon as possible, to avoid consequences including development of drug resistance and life-threatening toxicity (as have been reported with Reyataz and Viread, and Videx and ribavirin, respectively).

Pre-approval trials can address concerns usually dealt with in post-marketing commitments, through diverse enrollment and a more through portfolio of pharmacokinetic and drug-drug interaction studies. Regulators need larger, more tempting carrots and sharper sticks to incentivize and enforce more thorough pre-marketing studies, and prompt initiation of post-marketing commitments.

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