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Future Directions in the Marketing of Human Immunodeficiency Virus Treatments

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This year marks a decade since the advent of highly active antiretroviral therapy (HAART), combinations of human immunodeficiency virus (HIV-1)–fighting medications which have effectively transformed this disease from a death sentence into a chronic, largely manageable illness in developed countries. In 1995 and 1996, the introductions of the first protease inhibitors (PIs) were pivotal in instigating a precipitous decline in the onset of acquired immunodeficiency syndrome (AIDS).

Individuals with HIV who exhibit near-perfect adherence with their antiretroviral (ARV) medication regimens and remain free of resistant virus and medication-related toxicities can now expect to live a normal lifespan. As a result of the expansion of the ARV therapeutic category over the past 10 years, as well as the rapid evolution of therapeutic approaches in HIV medicine, pharmaceutical manufacturers are asking similar questions in planning their in-line marketing strategies.

- How is the treatment of HIV likely to evolve over the next five to 10 years? What are the key drivers of this transformation?
- What clinical attributes will determine whether new products succeed, given changing market conditions?
- What opportunities exist for companies to maintain and/or achieve a leadership position in the HIV market?

The Current Pharmaceutical Market

Available Medications. The recent additions of Gilead Sciences' (Foster City, CA) Truvada (emtricitabine/tenofovir disoproxil fumarate) and Philadelphia-based GlaxoSmithKline's (GSK's) Epzicom (abacavir/lamivudine) have brought the number of FDA-approved ARV medications to 25. These drugs are divided into five classes: (1) nucleoside analog reverse transcriptase inhibitors (NRTIs), (2) PIs, (3) non-nucleoside reverse transcriptase inhibitors (NNRTIs), (4) nucleotide analog reverse transcriptase inhibitors, and (5) fusion inhibitors.

A Large but Static Market. According to IMS Health (Plymouth Meeting, PA), the size of the worldwide ARV market in 2004 was approximately $7.3 billion, with the United States accounting for $4.5 billion. Whereas the first few years after the introduction of the PIs showed furious growth in sales and new prescription usage as patients sought to take advantage of these breakthrough medications, the past three to four years have seen a slowing in ARV sales growth.

Epidemiology and Treatment. The United Nations estimates between 36 million and 44 million individuals worldwide are infected with HIV, the majority of whom reside in sub-Saharan Africa. The Centers for Disease Control and Prevention (CDC) estimates that 850,000 to 950,000 Americans are living with HIV, including 180,000 to 280,000 who are unaware of their infection. The number of new annual infections in the United States are approximately 40,000 per year.

The advent of ARV therapy 10 years ago led to a decline in the number of new AIDS cases and AIDS-related deaths in Western countries. Nevertheless, certain geographic markets in the United States have witnessed a recent surge in the number of new HIV cases. One factor contributing to growth in new cases may include a perception that HIV is highly treatable and therefore no longer a serious illness.

Between 300,000 and 350,000 patients in the United States take ARV therapy. Current treatment guidelines call for a combination-therapy approach to HIV/AIDS. For naïve and earlier-stage patients, the guidelines call for regimens involving two members of the NRTI class and either an NNRTI or a PI as the third agent. As patients fail successive regimens, these guidelines suggest the use of molecular diagnostic assays to guide therapeutic selection. Patients who have failed multiple regimens often must take larger combinations of four to five ARV treatments to maintain viral suppression and uphold their immune system. At these later stages, many physicians incorporate unique agents, such as the fusion inhibitor Fuzeon (enfuvirtide), developed by Roche Laboratories in Nutley, New Jersey.

New Therapies on the Horizon. Data from Pharmaceutical Research and Manufacturers of America, Washington, DC, indicates 79 medications and vaccines are in clinical development for the treatment of HIV/AIDS and HIV-related opportunistic infections and cancers, including 34 new antiviral compounds. Several of these drugs will be available within three to four years, and represent important new ARV classes. New ARV classes that are expected to reach the market include entry inhibitors, integrase inhibitors, and maturation inhibitors. The Table lists most of the investigational ARV medications in phase 2 and 3 clinical development.

Major Trends in Therapeutic Management

Five trends and challenges shape the future HIV/AIDS therapeutic management landscape.

Simplification of ARV Regimens. One of the most important trends in the management of HIV is that ARV regimens are becoming simpler and more tolerable. Earlier HAART regimens were complicated, requiring patients to take a significant number of pills with complex dosing schedules, strict food- and water-intake timing, while dealing with substantial side effects. Newer medications afford the benefits of fewer pills per dosing interval, once-a-day dosing, flexible anytime-during-the-day dosing, and fewer side effects.

The ARV medications currently achieving the greatest sales and marketshare, particularly among patients in earlier lines of treatment, are those which accommodate the lifestyle of the patient, i.e., those with fewer side effects and a convenient dosing schedule (less dosing intervals, fewer pills, and flexible dosing intervals). New ARVs will be challenged to be even more patient friendly. These trends will favor the development of once-daily, highly tolerable, and coformulated ARVs.

Recognition of Toxicities. Side effects and adverse events linked to ARVs range from gastrointestinal disturbances, peripheral neuropathy, and central nervous system abnormalities, to metabolic abnormalities ranging from hyperlipidemia, hypertriglyceridemia, insulin resistance, and body-disfiguring morphologic changes (liposystrophy).

These side effects were more acceptable in the early stages of HAART when ARV therapies were rescuing patients from death. However, the evolution of HIV/AIDS into a chronic, manageable illness has decreased physicians'

TABLE: PHASE 2 AND 3 INVESTIGATIONAL ANTIRETROVIRAL MEDICATIONS

Compound / Class	Manufacturer	Development Status
AG-1859 (PI)	Pfizer Inc	Phase 2
AMD070	AnorMED	Phase 2
Beta-L-Fd4C (NRTI)	Achillion Pharmaceuticals	Phase 2
Calanolide A (NNRTI)	Sarawak MediChem	Phase 2
Capravirine (NNRTI)	Pfizer Inc	Phase 2
Elvucitabine (NRTI)	Achillion Pharmaceuticals	Phase 2
GSK-873 (Entry Inhibitor)	GSK	Phase 2
MIV-310	Medivir	Phase 2
PA-457 (maturation inhibitor)	Panacos Pharmaceuticals	Phase 2
PRO 542 (entry inhibitor)	Progenics Pharmaceuticals	Phase 2
Racivir	Pharmasset	Phase 2
Reverset (NRT)	Incyte	Phase 2
SCH-D (entry inhibitor)	Schering-Plough	Phase 2
SPD754 (NRTI)	Shire Pharmaceuticals	Phase 2
Tipranavir (PI)	Boehringer Ingelheim	NDA submitted
TMC114 (PI)	Johnson & Johnson	Phase 2
TMC125 (NNRTI)	Johnson & Johnson	Phase 2
UK-427,857 (entry inhibitor)	Pfizer Inc	Phase 2

PI = Protease inhibitor; NRTI = nucleoside analog reverse transcriptase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; GSK = GlaxoSmithKline; NDA = new drug application.
Adapted from HIVandHepatitis.com data.

and patients' tolerance of side effects. Thus, new ARVs will need to eliminate adherence-threatening nuisance side effects (such as GI side effects) and spare organ deterioration so that patients can take them safely over the long term.

The Spectre of Viral Resistance. The rapid emergence of resistance to ARV medications contributes to transient viral responses to subsequent regimens, which poses a risk of disease progression when patients expire all current therapies. Although several potent ARV medications are capable of overcoming moderately resistant virus, particularly Abbott's Kaletra (lopinavir/ritonavir) and Roche's Fuzeon, (enfuvirtide) one important implication for pharmaceutical companies is that new medications are needed that will overcome resistant virus, particularly in the salvage setting (where patients have few, if any, ARV medications to which their virus still is sensitive). Physicians frequently cite the unmet need for medications that overcome resistant virus and are also reasonably tolerable and convenient, thereby facilitating patient adherence. This is the setting in which physicians will be particularly receptive to ARVs with new mechanisms of action and/or ARVs in existing classes whose resistance profile allows them to combat virus with multitudes of accumulated viral mutations.

Increased Recognition of Co-infection. Approximately one-third of individuals living with HIV/AIDS are co-infected with hepatitis C (HCV), a virus which may result in end-stage liver disease. The threat of HCV has emerged as a clinically salient mortality threat. As of this writing, only Roche Laboratories' Pegasys/Copegus (pegylated interferon alfa-2a/ribavirin) was FDA approved for the treatment of HCV in HIV/HCV co-infected patients.

Approximately 5% of HIV-infected individuals in Western countries are co-infected with hepatitis B (HBV). Several ARVs used in the management of HIV have been effective in (although not in all cases FDA approved for) treating HBV, including GSK's Epivir (lamivudine), and Gilead Science's Viread (tenofovir) and Emtriva (emtracitabine).

The treatment of HIV/HCV and HBV co-infection represents an important opportunity for the development of new medications. The prevalence of HIV/HCV and HBV co-infection challenges manufacturers to develop effective ARVs which are less hepatotoxic.

A Curable Disease? A growing public perception holds that HIV/AIDS is a curable disease, especially as a result of the availability of effective therapy. This incorrect perception may be responsible for the recent resurgence in new infections as well as a greater degree of apathy toward recognized preventive measures.

From the perspective of diagnostic manufacturers, a demand has grown for genotypic and phenotypic assays to guide the optimization of treatments in highly resistant virus. New technologies will be needed to prevent immunologic decline through the optimization of therapies based on a more exact calculus not only of genotypic and phenotype patterns, but also regarding the complex interactions among ARVs.

The New Patient With HIV

The population first affected by the HIV virus was homosexual males. However, the epidemic increasingly has spread into racial and ethnic minorities. Non-Caucasian Americans now represent the majority of new AIDS cases and of those living with AIDS in this country. However, African Americans and Latinos represent 12% and 13% of the U.S. population, respectively, but they accounted for 47% and 19%, respectively, of newly reported AIDS cases in 2001, according to CDC data.

One quarter of the 800,000 to 900,000 Americans living with HIV/AIDS are women. Females with AIDS comprise a growing proportion of the U.S. HIV/AIDS epidemic. In 1992, women accounted for an estimated 14% of adults and adolescents living with AIDS; the latest data indicate that this percentage has increased to 22%. African-American and Hispanic women together comprise 25% of all U.S. females, however, they accounted for 83% of AIDS diagnoses reported in 2003.

The implications for manufacturers are that the populations into which the disease is spreading are less likely to be aware that they are infected, and thus less likely to seek treatment before the manifestation of symptomatology such as an opportunistic infection. From the perspective of in-line ARV marketing, communicating and disseminating information among the emerging populations remains a challenge. The homosexual population reacted by building educational and treatment infrastructures. However, minority populations affected by HIV are generally less educated and/or indigent. Additionally, whereas the stigma of HIV has largely been lifted among members of the homosexual community, HIV continues to represent shame in these emerging populations, preventing many individuals from seeking testing, treatment, and adhering to medications.

Manufacturers therefore should consider methods of appropriately targeting the emerging populations with prevention and treatment messages. Many pharmaceutical companies work with churches, inner-city clinics, and other institutions to communicate such messages. One of the most effective and highly visible campaigns is GSK's Magic Johnson ads; they have inspired many individuals to be tested and treated.

From a clinical development perspective, the shift of HIV into minority populations underlines the need for manufacturers to generate medications offering ease-of-usage, fewer pills, less overt side effects, less dosing intervals, no need for food or water intake requirements, and/or lack of refrigeration. This will permit individuals to unobtrusively

store and take their medications. Additionally, an unmet need has been noted for an effective, once-daily regimen for first-line female patients of child-bearing age that will not harm their baby should they elect to get pregnant.

Conclusion

The development of ARV medications dramatically curtailed morbidity and mortality associated with this illness. However, challenges still exist, and clinically significant opportunities for manufacturers remain. The main unmet need in the marketplace is primarily for "invisible" ARV medications, such as those that are convenient, free of side effects and long-term adverse event potential, yet have a sufficiently high resistance barrier to accommodate the inevitable human mistakes of missing doses.

Since existing regimens are effective in reducing viral load and maintaining viral suppression, therapies considered for use in initial treatment will be judged primarily upon the extent to which they are convenient, tolerable, safe, and compatible with other ARVs. Among patients who are highly treatment experienced, there is a clinically important need for novel medications that can overcome resistant virus, especially medications that can offer fewer side effects, reduced dosing frequency, as well as reduced pill burden.

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