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Review

Running a tightrope: Regulatory challenges in the development of antiretrovirals☆

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ABSTRACT

Since the approval of Retrovir, (zidovudine, AZT) in 1987 by the Food and Drug Administration, a number of regulatory initiatives were codified into regulation which contributed to the rapid development of new treatments for HIV-1 infection. These initiatives are a testament to the efforts of AIDS activists and regulators to improve access to drugs for serious and life-threatening diseases. Currently, 28 antiretroviral drugs and combinations of antiretrovirals are available to treat HIV-1 infection. The broadening armamentarium of approved antiretroviral drugs provides new options and more choices for physicians and HIV patients. Importantly, the introduction of these newly approved HIV drugs has shown that the majority of HIV-1-infected treatment-naïve and treatment-experienced patients can achieve maximal virologic suppression (less than 50 copies/mL HIV-1 RNA). This article describes the past and current regulatory challenges in the development of new HIV treatments and provides an overview of the drug regulations that were required for the approval of HIV drugs.

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Contents

☆ Disclaimer: This document is not meant to represent a Guidance or official FDA policy. The FDA has Guidances for nonclinical pharmacology-toxicology and virology studies, clinical guidances and information on the PreIND process. Sources for Guidances: http://www.fda.gov/RegulatoryInformation/Guidances/default.htm (assessed July 6, 2009); http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm (assessed July 6, 2009); http://www.fda.gov/Drugs/[DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/ucm077776.htm] (assessed July 6, 2009).

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1. Background

With the current availability of 28 antiretroviral (ARV) drug products and combinations of ARVs to treat HIV-1 infection (Table 1), it may not be easy to recall the fateful days of the AIDS crisis in the late 1980s and the despair of an AIDS diagnosis as an almost certain "death sentence". The advent of Retrovir (zidovudine, AZT) approval by the Food and Drug Administration (FDA) brought new hope in 1987. In that same year, the AIDS Memorial Quilt was displayed for the first time on the National Mall in Washington, D.C., covering a space larger than a football field with 1920 panels. The display garnered an overwhelming response and raised awareness of the devastating impact of AIDS. ACT UP was also formed in 1987 to respond to the mismanagement of the AIDS crisis and to protest the high cost of AZT. The hope that AZT would cure AIDS began to wane as many patients began developing resistance and experiencing treatment failure. The following year, ACT UP protests shut down the FDA to fight for access to new AIDS drugs. Subsequently, the FDA began a policy to expedite public access to AIDS drugs that were still in clinical trials.

After AZT, the approval of other nucleoside analog reverse transcriptase inhibitors (NRTIs), didanosine (ddI), zalcitabine (ddC), and stavudine (d4T), were welcomed but led to sequential monotherapy as standard-of-care. By 1992, AIDS had become the leading cause of death for men ages 25–44 years in the U.S. with an estimated 33,590 United States residents dying from HIV infection that year (CDC MMWR, 1993). In 1995, the first protease inhibitor (PI), saquinavir, was approved. This same year, several clinical trials showed that using two anti-HIV drugs together was better than using one (Darbyshire et al., 1996; Hammer et al., 1996; Saravolatz et al., 1996). Soon after in 1996–1997, the treatment breakthrough of using three drugs together, highly active antiretroviral therapy (HAART), led to levels of HIV-1 RNA below the limits of assay detection. AIDS-related deaths in the U.S. markedly declined. With the use of HAART regimens, AIDS-related mortality in the U.S. decreased from 29.4 deaths per 100 person-years in the first quarter of 1995 to 8.8 deaths per 100 person-years in the second quarter of 1997 (Palella et al., 1998). However by 2002, despite this decline, AIDS had become the leading cause of death worldwide for people aged 15–59 years (WHO, 2003).

Although the availability of HAART was remarkably successful in reducing AIDS morbidity and mortality (Hammer et al., 1997; Palella et al., 1998), HAART had and continues to have serious side effects such as neuropathy, lipodystrophy, and liver toxicity. In addition, initial HAART regimens were complicated with multiple large pills taken up to three times a day, which if not taken properly resulted in resistance development and treatment failure. Treatment failure and intolerance to drug treatment continued to grow underscoring the need for new potent AIDS drugs and combinations of drugs with easier regimens.

Throughout this decade, the HIV drug pipeline flowed with new potent HIV drugs and combinations, once-a-day formulations and drugs that had novel targets. The broadening arsenal of approved HIV drugs provided new options and importantly more choices for physicians and HIV patients. The first combination ARV formulation, lamivudine and zidovudine (Combivir), was approved in 1997 and then throughout 2000–2006, 11 new drugs and combinations were approved. The first generics of ddI and AZT were also approved in 2004 and 2005. A major advance in July 2006 was the approval of Atripla – a one pill, once-a-day combination of efavirenz, tenofovir disoproxil fumarate (DF), and emtricitabine option for treatment-naive patients. Additionally, with the pressure to develop drugs for treatment-experienced patients, several drugs were studied in and approved for treatment-experienced patients – enfuvirtide (T20), tipranavir (TPV) and darunavir (DRV). The approval of these drugs provided much needed options for treatment-experienced patients. In 2007 and 2008, three new molecular entities maraviroc, raltegravir and etravirine were approved leading to dramatic changes in the management of treatment-experienced patients. Maraviroc and raltegravir were the first members of new classes of drugs targeting the CCR5 co-receptor needed for HIV entry and viral integrase, respectively. The introduction of these newly approved ARVs has shown that the majority of treatment-experienced patients can achieve maximal virologic suppression and current guidelines now recommend that the goal of ARV therapy in treatment-experienced patients is less than 50 copies/mL HIV-1 RNA.

Throughout this harrowing and momentous period of time, a number of regulatory initiatives fought for by AIDS activists and regulators were codified and contributed to the accelerated development of new treatments for HIV-1 infection. This article describes the past and current regulatory challenges for the development of new HIV treatments and as necessary provides an overview of United States drug regulations that were required for the approval of HIV drugs.

Table 1
Antiretroviral drug products and combinations of ARVs to treat HIV-1 infection.

Drug name	U.S. Approval date
Retrovir zidovudine	March 1987
Videx (didanosine)	October 1991
Hivid (zalcitabine)	June 1992
Zerit (stavudine)	June 1994
Epivir (lamivudine)	November 1995
Invirase (saquinavir)	December 1995
Norvir (ritonavir)	March 1996
Crixivan (indinavir)	March 1996
Viramune (nevirapine)	June 1996
Viracept (nelfinavir)	March 1997
Rescriptor (delavirdine)	April 1997
Combivir (lamivudine and zidovudine)	September 1997
Fortavase (saquinavir Soft Gel Cap)	November 1997
Sustiva (efavirenz)	September 1998
Ziagen (abacavir sulfate)	December 1998
Agenerase (amprenavir)	April 1999
Kaletra (lopinavir/ritonavir)	September 2000
Trizivir (abacavir sulfate, zidovudine and lamivudine)	November 2000
Viread (tenofovir DF)	October 2001
Fuzeon (enfuvirtide)	March 2003
Reyataz (atazanavir)	June 2003
Emtriva (emtricitabine)	July 2003
Lexiva (fosamprenavir)	October 2003
Epzicom (abacavir sulfate and lamivudine)	August 2004
Truvada (tenofovir DF and emtricitabine)	August 2004
Aptivus (tipranavir)	June 2005
Prezista (darunavir)	June 2006
Atripla (efavirenz, tenofovir DF, and emtricitabine)	July 2006
Selzentry (maraviroc)	June 2007
Isentress (raltegravir)	October 2007
Intelence (etravirine)	January 2008

2. Evolution of drug regulations to address the HIV/AIDS epidemic

When regulating drugs to treat life-threatening diseases such as HIV-1 infection, the need for access must always be balanced with the quantity of data needed to support the clinical use of drugs. The FDA strives to provide access to potentially life-saving drugs as soon as possible while attempting to obtain crucial information so that the drugs may be used safely and efficaciously. For marketing approval, the FDA requires that a drug be studied in adequate and well-controlled trials to provide sufficient safety and efficacy data to inform its clinical use in the intended population. Therefore, the FDA must balance the need for early access to a drug while not jeopardizing the ability to attain safety and efficacy data on the drug through controlled clinical trials. Many of the regulatory

mechanisms developed to accelerate drug approval and increase access to life-saving drugs deal with the competing issues of providing therapies quickly, while at the same time ensuring that the necessary clinical research can be completed to characterize safety and efficacy.

Prior to the AIDS epidemic, regulations such as Emergency Investigational New Drug (IND) applications, and Group C INDs allowed for increased flexibility and early access in overall drug approval, but the scope of these regulations was not considered broad enough to deal with the AIDS epidemic. Group C INDs applied only to cancer drugs administered through the National Cancer Institute. Emergency INDs usually involve administration of drug to a single patient in situations that do not allow time for submission of an IND in the usual manner. In 1988, Title 21, Part 312, Subpart E regulations facilitated earlier access to medications and biologics for life-threatening or severely debilitating diseases by allowing for a 'treatment protocol' prior to marketing approval in situations where the preliminary analysis of phase 2 trials was promising (U.S. Food and Drug Administration, Code of Federal Regulations, Title 21, Part 312, Subpart E, revised 2009). However, largely as a response to the HIV epidemic and pressure from AIDS activists, the FDA codified additional regulations to allow access and expedite drug development for life-threatening diseases. These included regulations for accelerated approval, expansion of pre-approval access to drugs for patients in need of new therapeutic options, and optimized procedures for interactions between the agency and pharmaceutical sponsors. While these terms are often confused and may seem irrelevant to clinicians, most of the anti-HIV drugs used in routine clinical practice were approved under these regulations or as test cases before these regulatory policies were codified. For example the didanosine early access program and approval served as a model for the accelerated approval regulations.

2.1. Accelerated approval

Under accelerated approval, codified in 1992 at Title 21, Part 314, Subpart H of the U.S. Code of Federal Regulations, drugs that have been studied for their safety and efficacy in treating serious and or life-threatening illnesses and provide meaningful therapeutic benefit to patients over existing treatments can be approved based on clinical trials that evaluate a surrogate endpoint rather than the traditional endpoints of irreversible morbidity or mortality (U.S. Food and Drug Administration, Code of Federal Regulations, Title 21, Part 314, Subpart H, revised 2009). The FDA may grant marketing approval for a new drug product based on clinical trials establishing that the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on the basis of an effect on a clinical endpoint other than irreversible morbidity or mortality. Thus, clinical trials can be completed in a shorter period of time, and drug approval can be expedited. Under accelerated approval, marketing of a new drug is subject to certain conditions such as the requirement to provide confirmatory data post-marketing to show long-term clinical benefit, FDA review of all advertising materials, and expedited drug withdrawal procedures if clinical trials fail to confirm efficacy post-marketing. Once clinical efficacy is confirmed in clinical trials post-marketing, a drug originally approved for marketing under accelerated approval may be granted "traditional" approval, which is the usual regulatory approval for drugs used to treat most medical illnesses. Other characteristics such as improved safety may constitute a meaningful therapeutic benefit and justify accelerated approval.

2.2. Viral load as a surrogate endpoint

One of the initial challenges dealt with in the implementation of the accelerated approval process was determining and validating a surrogate endpoint for clinical trials of HIV drugs. The approval of the first antiretroviral, AZT, was based on clinical endpoints. However, criticism of the clinical endpoint trials mounted as patients had to remain on randomized treatment regimens until a clinical endpoint such as a new opportunistic infection or death occurred. Marketing approval of new treatments was delayed waiting for clinical endpoint trials to be completed. With the availability of potent antiretroviral drug regimens and sensitive assays for quantifying plasma HIV-1 RNA, the standards of clinical practice evolved to emphasize maximal and durable HIV-1 RNA suppression. Compared with an endpoint of disease progression, using plasma HIV-1 RNA as a surrogate marker had practical advantages including: routine use in clinical practice, ease of measurement, patient acceptability, earlier evaluation of drug activity, the opportunity to rapidly identify loss of response and the economy of sample size. Given that HIV-1 RNA testing was available and investigators and patients could monitor HIV-1 RNA outside the clinical trial and make individual treatment decisions based on HIV-1 RNA tests, the ethics of mandating patients remain on "failing" regimens to collect clinical endpoints was questioned.

In July 1997, the Agency convened an advisory committee meeting to consider the use of changes in HIV-1 RNA levels as endpoints in clinical trials supporting traditional approval of antiretrovirals (U.S. Food and Drug Administration, Antiviral Advisory Committee transcripts, July 14-16, 1997). To evaluate the feasibility of using HIV-1 RNA levels as an endpoint, a collaborative group of pharmaceutical, academic, and government scientists investigated relationships between treatment-induced changes in HIV-1 RNA and clinical endpoints from ongoing and completed antiretroviral trials. In several analyses of more than 5000 patients in multiple trials, a clear association was identified between initial decreases in plasma HIV-1 RNA levels and reduction in the risk of clinical progression and death (Murray et al., 1999; Hill et al., 1998). This relationship was observed across a range of patient characteristics including pretreatment $CD4^+$ cell counts and HIV-1 RNA levels, prior drug experience, and treatment regimen. Based on these data, the FDA Antiviral Advisory Committee concurred that treatment-induced decreases in HIV-1 RNA levels were highly predictive of meaningful clinical benefit and that HIV-1 RNA measurements could serve as endpoints in trials designed to support both accelerated and traditional approvals. The Division proposed that accelerated approvals could be based on trials that show a drug's contribution towards shorter-term reductions in HIV-1 RNA (e.g., 24 weeks) while traditional approvals could be based on trials that show a drug's contribution towards durability of HIV-1 RNA suppression (e.g., for at least 48 weeks). The committee agreed with this proposal and also recommended that changes in $CD4^+$ cell counts be consistent with observed HIV-1 RNA changes when considering approval of an antiretroviral drug. After 1997, the FDA allowed clinical confirmation of accelerated approval to be accomplished by showing sustained reduction in viral load measurements. This work led to feasible, ethical clinical trial designs and paved the way for future antiretroviral drug development.

With accelerated approvals of drugs for HIV-1 infection, the same trials used for the initial surrogate endpoint analyses were usually continued for the collection of clinical endpoints and to assess longer term virologic endpoints. Often, by the time the surrogate data were collected, analyzed, and submitted to regulatory agencies, the clinical endpoint portion or virologic durability portion of the trial was well underway and sometimes nearing completion. Confirmatory trials were negotiated with regulatory agencies well in advance of data submission for accelerated approval, so plans for clinical confirmation of antiretrovirals were generally in place at the time of initiation of phase 3 trials.

2.3. Fast Track

The development and approval of protease inhibitors occurred using procedures to expedite the approval process such as frequent agency/industry interactions, rolling submission of data to the agency, and prioritization of resources for rapid reviews. These provisions, which the agency had already been using for approval of antiretroviral drugs such as PIs, were codified as Fast Track designation in the Food and Drug Modernization Act (FDAMA) of 1997 (U.S. Food and Drug Administration Modernization Act of 1997). Fast Track allows for increased face-to-face interactions between a drug sponsor and FDA during development, and also allows for "rolling" submission of data prior to submission of a complete new drug application (NDA). Fast Track designation ensures consideration, but not necessarily a guarantee, of a priority review. Under current legislation, a priority review means that FDA has agreed to take an action within 6 months rather than within 10 months, the latter being the time required for a standard review.

3. Clinical trial designs

Approval of new drugs for marketing by the FDA is usually based on at least two adequate and well-controlled trials. Under accelerated approval, antiretroviral trials typically assess virologic efficacy at 24 weeks as a surrogate endpoint. Analyses at earlier time points (e.g., 16 weeks) have proven less discriminating in detecting important differences between treatment regimens, but have been used on some occasions. To support traditional approval and treatment-naïve indications, trials are conducted for 48 weeks or longer.

The complexity of HAART therapies has created unique challenges for designing clinical trials, because it has sometimes been difficult in clinical trials to distinguish the safety and efficacy of a new drug from other drugs in the regimen. Each additional drug in a regimen increases the potential for overlapping toxicities, pharmacologic interactions, or other biologic interactions (e.g., synergy or antagonism) that may obscure the evaluation of a particular drug. Even in the absence of such interactions, assessing comparability of two drugs as part of a HAART regimen can be a challenge depending on the patient population studied and the expected potency of the particular drugs to be compared. For example, choosing an appropriate active control arm, particularly in studies evaluating treatment-experienced patients with few remaining options, can be problematic. Given these challenges, it is critical that clinical trials be designed such that the contribution of a new antiretroviral toward efficacy can be unequivocally demonstrated. This requirement has been accomplished in the approval of many HIV drugs by using superiority trial designs. In the superiority trial design, the new drug is added to an optimized background ARV regimen and shown to be superior compared to an optimized background ARV regimen plus placebo.

Trials designs for treatment-naïve and treatment-experienced patients have evolved and continue to evolve as patient populations change and new ARVs become available.

3.1. Treatment-experienced patient trials

Prior to 2000, controlled HIV trials were largely conducted in treatment-naïve or patients with prior exposure to only the NRTI class of medications. As a result data in patients previously exposed to multiple classes of medications (heavily treatment-experienced patients) were limited. In 2001, the FDA's Antiviral Drugs Division held a Advisory Committee meeting to discuss clinical trial design issues in heavily treatment-experienced patients and issued the final "Guidance for Industry: Antiretroviral Drugs Using Plasma HIV RNA Measurements – Clinical Considerations for Accelerated and Traditional Approval" in 2002 (U.S. Food and Drug Administration Antiviral Drugs Advisory Committee transcript, January 11, 2001; U.S. Food and Drug Administration Guidance, 2002). Following this meeting and several other meetings with advocates and researchers on the issues of treating heavily treatment-experienced patients, a new emphasis was placed on clinical trials in this population leading to improvements in management of these patients and new clinical trial strategies. Resistance testing technologies were validated for clinical use and became standard-of-care in choosing new regimens with at least two active ARV drugs. Throughout the 2000s, new drugs for HIV-1 infection were tested in three-drug class experienced patients.

To minimize risk in clinical trials enrolling heavily treatment-experienced patients, provisions were made in trial designs to allow for early switch to the investigational agent arm for those trial participants in the control arm not achieving or maintaining a virologic response. However, cross-over options for patients who experience virologic failure created complex efficacy and safety assessments. In several drug development programs in heavily treatment-experienced patients (e.g., enfuvirtide and tipranavir), the cross-over clinical trial designs led to a declining number of subjects in the control arm (Chan-Tack et al., 2008; Struble et al., 2005). Therefore, there was the potential for systematic bias because of lower exposure of the control arm in comparison with the new drug arm. Patients who switched from the control group to the investigational arm may have been those who had advanced disease and were not responding to therapy. Given that adverse events often occur with increased frequency in patients with lower $CD4^+$ cell counts, imbalances due to switches from control to investigational agent could cause bias (Struble et al., 2005). One approach the FDA used to adjust for this potential bias was to assess adverse event rates per 100 patient-years.

With the approval of three new ARVs in 2007 and 2008, the management of heavily treatment-experienced patients dramatically changed. With these new agents, achieving HIV RNA <50 copies/mL is possible for the majority of these patients. In January 2008, the Forum for Collaborative HIV Research (FCHR) in collaboration with the FDA and European Medicines Agency (EMEA) held a meeting to discuss designing trials for treatment-experienced patients in the new era of multiple treatment options (Chan-Tack et al., 2008). During the meeting, consensus was reached that the recommended primary efficacy endpoint for clinical trials in treatment-experienced patients is achieving HIV-1 RNA less than 50 copies/mL. Another principal agreement at the meeting was to minimize the risk of patients receiving suboptimal therapy (i.e., functional monotherapy) which facilitates the rapid development of drug resistance.

Non-inferiority trial designs in trials of new ARV drugs were discussed at the Forum for Collaborative HIV Research meeting. Due to the availability of a number of efficacious therapeutic options for many patients, superiority trial designs are becoming less feasible. The challenge in non-inferiority designs is identifying a justifiable non-inferiority margin, which is the proportion of the efficacy of the active control drug which must be preserved. This first requires quantitatively establishing the efficacy contribution of the active control drug within the comparator regimen. In ARV trials, it can be challenging to precisely estimate the contribution of individual drugs in a HAART regimen towards an overall virologic response. The FDA has analyzed study data from previous clinical trials and asked sponsors to analyze study data from ongoing clinical trials in order to establish the efficacy of the active control drug within a regimen. Reliable estimates of treatment effects including confidence intervals are necessary. Considering baseline resistance profiles in establishing the efficacy of the active control is another challenge. In

addition, non-inferiority trial designs assume "constancy", meaning that the non-inferiority trial should be as similar as possible to the historical trial that established the efficacy of the active control compared with placebo.

Recognition that there is heterogeneity in treatment-experienced patients has been critical when designing trials in treatment-experienced populations. Treatment goals for patient populations with limited prior treatment experience and drug resistance are approached differently than treatment goals for patients with extensive prior treatment experience and drug resistance. Patients with first treatment regimen failure generally have several treatment options so the goal of therapy remains complete suppression of HIV-1 RNA. However, patients with multiple regimen failures and resistance to multiple drug classes have limited if any treatment options and the goal of therapy is to prevent clinical progression and preserve immune function while awaiting new treatments.

The use of genotypic and phenotypic resistance data has become essential in constructing optimized ARV background regimens (OBR) for trials in treatment-experienced patients and in identifying active ARV drugs for subsequent treatment regimens. Historically, patients were classified as 'one-drug', 'two-drug', or 'three-drug class resistant. Today the definition has evolved to reflect the number of active ARVs or drug classes currently available to a patient. This new approach is consistent with current DHHS treatment guidelines that recommend two or preferably three fully active agents to minimize the risk of virologic failure and resistance that may occur in patients with one or no active ARVs in their regimen. The 24-week data from etravirine, maraviroc and raltegravir Phase 3 trials highlight that response rates increase as the total number of active drugs in the regimen increased and stress again the importance of having at least two active agents in a regimen (Etravirine, 2008; Maraviroc, 2007; Raltegravir, 2007). It has consistently been demonstrated in multiple clinical trials, more active drugs, ideally three or more, in a regimen increases the probability of viral suppression (Steinbigel et al., 2008; Cooper et al., 2008; Madruga et al., 2007; Lazzarin et al., 2007; Etravirine, 2008; Maraviroc, 2007; Raltegravir, 2007).

3.2. Treatment-naïve patient trials

Early in HIV drug development, only approximately 2% of treatment-naïve patients receiving only two nucleoside analogs achieved a HIV-1 RNA below the 400 copies/mL assay detection limit. Beginning in 1995, suppressing HIV-1 RNA below assay detection limits and long term suppression beyond 24 weeks were a new phenomenon, recognized when PIs and NNRTIs became available and were added to a dual nucleoside backbone. The addition of a PI or an NNRTI to two nucleosides dramatically improved a negligible viral load response of <2% to a response rate of 60–90%, owing to the potency of PIs and NNRTIs, marked antiretroviral synergy, and a greater genetic resistance barrier that three drugs confer compared to two drugs.

Today, treatment-naive patients have more ARV options available than ever before to construct a safe, tolerable, effective and durable regimen. Improving on the established efficacy of 70–85% achieving less than 50 copies/mL at week 48 in treatment-naive patients may be difficult (Chan-Tack et al., 2008). However, the need for ARVs for treatment-naïve patients still exists because other characteristics of ARVs can certainly be improved such as higher genetic barriers to resistance, fewer drug–drug interactions and fewer side effects such as gastrointestinal toxicities, rash and hepatotoxicity. Other areas for improvement include alternative pharmacokinetic boosters with better safety and tolerability profiles than ritonavir and more fixed dose-combination formulations to reduce pill burden. Traditionally for treatment-naïve patient trials, non-inferiority trial designs are used to evaluate safety and efficacy of a new ARV compared to an active control in combination with a fixed-background regimen. Little has changed in terms of trial designs for treatment-naïve patients; however, the timing of treatment-naïve trials has become an issue for discussion. At the January 2008 Forum for HIV Collaborative HIV Research meeting, trial design issues for treatment-naïve patients were discussed including the timing of treatment-naive trials in the overall development program. Several experts suggested treatment-naive patients may have greater risk and lower potential benefit if enrolled in trials with investigational agents instead of receiving standard-of-care (SOC) according to treatment guidelines (Chan-Tack et al., 2008). Other experts suggested treatment-naive patients could have overall lower risk from trial participation than treatment-experienced patients, as numerous active ARVs still remain if treatment-naive patients experience virologic failure and/or resistance. For a new class or recently approved classes, such as CCR5 coreceptor antagonists or integrase strand transfer inhibitors, some data from phase 2/3 trials in treatment-experienced patients may be informative prior to initiating treatment-naïve trials. Simultaneous drug development in treatment-naive and treatment-experienced patients is possible. However, this approach depends on the characteristics of each investigational drug and overall risk benefit profile for each population. Therefore, the timing of treatment-naive trials remains flexible and as always requires ongoing communication among researchers, industry and regulatory agencies about the issues of clinical trial design.

4. Confronting resistance and cross-resistance

In addition to intolerance to medication, suboptimal adherence, and drug interactions that reduce plasma drug concentrations, emergence of resistance to antiretroviral drugs is one of the more common reasons for HIV-1 treatment failure. After the approval of AZT, resistance quickly became an apparent problem. In early 1989, Larder and colleagues reported isolating resistant HIV-1 strains from five persons with AIDS who had been on AZT for a year or more (Larder et al., 1989). HIV-1 strains isolated from people on long-term AZT monotherapy showed 10- to 1,000-fold less susceptibility to AZT in tissue culture as compared to HIV-1 strains isolated before those individuals began taking AZT. After failure on AZT, sequential monotherapy using each subsequently approved drug (i.e., ddI, ddC, and d4T) became standard-of-care. The failure of sequential monotherapy in HIV infection reinforced the importance of maximizing barriers to drug resistance provided by the simultaneous administration of multiple drugs. HAART led to dramatically reduced levels of HIV-1 viral replication and raised the resistance barrier thus reducing treatment failures from developing resistance. Unfortunately, resistance to ARV drugs still occurred over time usually with the accumulation of multiple mutations.

For almost 20 years, only two viral gene products were targeted by the ARV drugs (i.e., reverse transcriptase and protease). Unfortunately, mutations conferring drug resistance that developed during therapy with NRTIs, NNRTI, and PIs frequently resulted in cross-resistance to other members in the same drug class. Although, there are numerous approved antiretrovirals from six drug classes, maintaining drug susceptibility for a lifetime of treatment is a critical issue. Accordingly, resistance testing in clinical trials to determine the effect of an antiviral drug on the evolution of viral resistance and to identify the baseline genotypic/phenotypic determinants of virologic success or failure is a key part of drug development.

In the late 1990s, rapid assessment of genotypic and phenotypic drug resistance became available. It became evident that genotypic

and phenotypic testing for HIV-1 resistance to ARV drugs would be beneficial for individual patient management when choosing an initial ARV regimen or changing therapy. Several trials demonstrated that virologic outcome may be improved when genotypic or phenotypic data are used to guide choice of drug regimens in patients with loss of virologic response to prior regimens (Baxter et al., 2000; Durant et al., 1999; Cohen et al., 2002; Meynard et al., 2002; Tural et al., 2002). However, the assays under development needed validation, standardization, and a defined interpretation for clinical use (Hirsch et al., 1998). Therefore, as a routine part of studying drug resistance in drug development, the FDA requests the use of reliable resistance assays in clinical trials and knowledge of the assay technical limitations and assay performance characteristics.

In order to independently analyze resistance data and characterize an ARV drug resistance profile, comprehensive clinical resistance testing is needed in all phases of drug development. Data from nonclinical trials and Phase 1 and Phase 2 clinical trials can provide a preliminary idea of the amino acid substitutions mutations that confer reduced drug susceptibility and a lack or loss of virologic response. Phase 3 trial designs incorporate this information and expand on it, thereby aiming to further characterize drug resistance and provide data on how to use the drug clinically. Longer term durability data on baseline genotype/phenotype relationships to virologic response can be obtained from Phase 4 post-marketing trials and continuing Phase 3 trials. The publication of the "Guidance for Industry Role of HIV Resistance Testing in Antiretroviral Drug Development in 2007" reinforced characterization of resistance and cross-resistance as a critical part of antiretroviral drug development, so clinical resistance data could be available at the time of drug approval in order to properly disseminate resistance information to health care providers (U.S. Food and Drug Administration Guidance, 2007).

The FDA Division of Antiviral Drug Products was confronted with significant challenges in reviewing resistance data. The challenges included the use of several different genotypic or phenotypic assays in clinical trials, different algorithms and interpretation of drug susceptibilities, and various formats for submitting genotypic and phenotypic data by each sponsor. Beginning in 2001, a systemized method of resistance data collection was requested of ARV drug sponsors including baseline phenotype and genotype samples on all trial patients. The "Guidance for Industry Role of HIV Resistance Testing in Antiretroviral Drug Development" outlined a systematic uniform way of submitting resistance data for easier and consistent review (U.S. Food and Drug Administration Guidance, 2007). Acquisition of these data allowed analyses of virologic outcome by baseline genotype or phenotype in order to assess the effect of baseline resistance. Analyses of responses by different baseline resistance profiles provide evidence of antiviral activity and important information for clinical use for physicians. Moreover, early determination of the effect of baseline genotype and phenotype for new investigational agents is often important for patient selection in clinical trials. Following a complete review of the available data, the resistance information provided in the package insert is valuable for physicians selecting antiretroviral drugs for patients with reduced susceptibility to other antiretroviral drugs and aids them in deciding on optimal treatment options for HIV-1 infection.

Genotypic and phenotypic susceptibility scores (GSS and PSS) represent the total antiviral activity of a combination ARV regimen, i.e., the number of active drugs in a regimen. These scores are useful when assessing the contribution of drugs to virologic response and when determining an optimized background regimen (OBR) in clinical trials. However, the complexity of the numerous different algorithms used for determining GSS and PSS scores also presents a challenge. Various methods have been used for calculating susceptibility scores. One typical method is a drug receives a score of "0" if there is evidence at baseline of reduced susceptibility or "1" if there is no evidence for reduced susceptibility in the baseline resistance test. However, with the variety of algorithms used to calculate GSS and PSS scores, it makes it difficult to compare OBR in different trials over time, the treatment-experience level of populations in different clinical trials, and efficacy based on baseline resistance across clinical trials. Furthermore, the addition of only one active drug to a failing regimen usually is not recommended because of the risk of developing resistance to that drug. Therefore, to ensure appropriate background ARVs are consistently selected for patients in trials and patient enrollment in clinical trials is consistent across trials, a systematic standardized approach to determine susceptibility scores and the number of active drugs, including the role of treatment history is needed. In the interim, the simplest and most conservative approach will most likely be used.

5. Improving access for patients with limited treatment options

5.1. Expanded access

Patients who have no remaining treatment options and are at imminent risk of disease progression secondary to severe immunodeficiency cannot wait for approval of new agents and may not be eligible for participation in randomized controlled registrational trials. Such patients may be able to access investigational therapies in expanded access programs or participate in open-label, compassionate-use safety trials. In these cases, single arm safety and tolerability endpoint trials can provide supportive safety data of the investigational drug in the overall development program.

Expanded Access is a general term that refers to several different mechanisms that allow drugs to be used for treatment prior to their approval (e.g., treatment INDs). With expanded access, a drug is made available to patients who have limited therapeutic options via protocols that are usually uncontrolled, open-label, and streamlined with respect to collection of safety and efficacy data. Expanded access mechanisms have generally been permitted when the product is well into clinical trials or when all clinical trials have been completed, after availability of evidence that the product is effective. One challenge with expanded access programs for PIs occurred in the late 1990s. There was limited supply of PIs prior to approval and thus limited access for desperate patients to these life-saving new drugs. Several companies had lotteries for the PIs which outraged patients. The FDA met with the community to hear their concerns about the limitations of expanded access programs and made specific efforts to discuss manufacturing capabilities and supply prior to or during phase 2 development. These efforts helped to ensure adequate supply of product to meet the expected needs for an expanded access program as well as the required drug development program.

Currently, it is regarded as unacceptable and unethical to randomize patients to receive a new investigational drug or placebo without protocol inclusion criteria that specify the number of active agents in the OBR; suboptimal treatment can lead to rapid development of drug resistance and not knowing whether one is receiving an active drug or placebo when constructing a regimen puts the participant at risk of losing further drug susceptibility to one or multiple drugs. However, despite new treatment options, we recognize a major obstacle still facing many treatment-experienced patients remains the availability of at least two active ARV drugs to construct a new active regimen. Thus designing randomized clinical trials for treatment-experienced patients with only one or no active ARV's for OBR continues to be a prevailing challenge. Prudent risk/benefit assessment should be made collaboratively by the patient and clinician/investigator for treatment-experienced

patients who are clinically stable but have ongoing HIV-1 replication despite optimized ARV therapy. Some patients, such as those with higher $CD4^+$ cell counts, could continue close clinical monitoring until at least two fully active ARVs are available to construct a new optimized regimen.

With the greater availability of approved treatment options, there has been decreased need for very early access to HIV drugs on a large-scale. Recently, smaller expanded access programs consisting of open-label protocols have been implemented to allow early access to promising drugs. However, it is recognized that there is a growing number of individuals who have exhausted available treatment options because of drug resistance and cross-resistance. Treatment IND and other expanded access mechanisms may be needed again in the future. The intent of all of these mechanisms is to allow early access to promising drugs without interfering with the ability of sponsors to complete clinical trials to support drug approval and adequate labeling.

5.2. President's emergency plan for AIDS relief (PEPFAR)

HIV-infected people around the world in resource-limited settings have had limited access to life-saving ARV treatments. In January 2003, President George W. Bush announced a 5-year $15 billion plan for emergency HIV/AIDS relief to targeted African, Asian and the Caribbean nations. This program was renewed in July 2008 with $48 billion including funding for the treatment of tuberculosis and malaria from 2009 through 2013 (United States President's Emergency Plan for AIDS Relief, PEPFAR Overview, 2009). PEPFAR (President's Emergency Plan for AIDS Relief) only allowed procurement of antiretroviral drugs approved by a "stringent regulatory authority", namely the FDA. However, the most commonly used drugs and fixed dose combinations in Africa were generic drugs not approved or available in the U.S. PEPFAR was criticized for allowing only single innovator products and not less expensive generic drugs and fixed dose combination drugs which were easier to distribute and facilitated adherence. The FDA can only approve generic drugs if there are no outstanding patents or exclusivity. However, most drugs for HIV-1 infection are under patent. The solution has been tentative approval, which meets all the standards of safety, efficacy and quality, but allows procurement for PEPFAR use regardless of remaining U.S. patents. In 2007, by buying generic ARVs, PEPFAR saved more than $70 million and was able to treat more people due to the cost savings (Holmes et al., 2009). As of 2008, the FDA has granted approval or tentative approval to 78 single entity generic antiretroviral drugs and fixed dose combination drugs and 2 million men, women and children infected with HIV/AIDS in 15 countries are receiving ARV treatment through PEPFAR (United States President's Emergency Plan for AIDS Relief, About PEPFAR, Treatment, 2009; United States President's Emergency Plan for AIDS Relief, Celebrating Life: Latest PEPFAR Results, 2009).

5.3. Pediatrics

Clinical trial data and dosing information for HIV-1 infected pediatric patients often lag behind adult information. Inadequate dosing information for HIV-1 infected children can result in subtherapeutic exposures and lead to development of resistance. Additionally inadequate dosing information could put children at risk for adverse reactions due to increased exposures. Developing age appropriate formulations for all pediatric age groups, including liquid preparations, chewable tablets, dispersible tablets and fixed dose combination preparations is important to provide access to life-saving therapies for HIV-1 infected children. Over the years, the FDA encouraged applicants to obtain pediatric labeling information (U.S. Food and Drug Administration 1994; U.S Food and Drug Administration, 1998; U.S Food and Drug Administration, 1999). Unfortunately, this approach did not always result in the development of age appropriate formulations or appropriate dosing recommendations for all children. The Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) provide mechanisms for the FDA to promote the collection of pediatric data (Best Pharmaceuticals for Children Act, 2002; Senate Report, 2001; McKinney, 2003; U.S. Food and Drug Administration Amendments Act, 2007). The Division discusses pediatric development plans with each sponsor throughout the development process and encourages trials in pediatric patients as early as possible. For HIV treatment, the Division typically requests multiple-dose pharmacokinetic, safety and activity data in patients from two to four weeks of age up to 18 years of age. In some cases, pharmacokinetic data in patients less than 2 to 4 weeks is also requested. The trials are designed to include an adequate number of patients to characterize pharmacokinetics and select a dose for the age ranges studied. The goal is to match drug exposures in children to known therapeutic exposures in adults. Although some challenges arise when choosing the best dose for children, knowledge of previous adult data across a range of doses/exposures with respect to safety, activity and resistance data aid in dose selection.

Overall, we have not observed major differences between HIV-infected pediatric patients and adults in the efficacy and safety of antiretroviral drugs. To date, the majority of antiretroviral products have some dosing information for pediatrics. Our goal is to provide product labeling and dosing information for treatment of HIV-infection in all pediatric ages groups as soon as possible based on the risk/benefit assessment from adult data. Numerous trials are ongoing to provide dosing information, especially for the newly approved antiretroviral agents. Table 2 summarizes the currently approved antiretroviral drugs for children for the treatment of HIV-1 infection.

6. Future challenges

HIV infection is viewed as a chronic infection. Despite the successes of treatment and prevention efforts, the rates of new HIV infections continue to rise globally. More HIV research today is focused on therapeutic prevention efforts such as development of topical vaginal/rectal microbicide and development of oral products.

The next challenge HIV research faces is the design, conduct and evaluation of therapeutic HIV prevention trials. For microbicide development, one challenge is the lack of a surrogate marker for prevention; therefore, proof-of-concept trials or dose finding trials during phase 2 development are not possible. Phase 2 trials are essentially expanded safety trials and evaluation of effectiveness is done in phase 3 trials. Funders of microbicide development are challenged by the large sample size needed to show effectiveness. Choosing an appropriate sample size is based on the ability to predict HIV infection rates in a given geographic area with precision. Preliminary trials have found the HIV infection rate was overestimated as intensive counseling efforts and condom provisions have led to lower HIV infection rates during trial conduct.

For several ongoing or completed phase 3 studies, the sample size calculations were based on 30–33% reduction in HIV acquisition. Lower reductions may have global impact on HIV transmission; however, the totality of the data must be taken into consideration before concluding a product should be available globally. Any reduction in HIV infection rates must be carefully weighed with the side effect profile, the potential for condom migration and increase in sexually transmitted diseases.

Another challenge in the microbicide field is the high rate of pregnancy in trials and the impact on efficacy and safety results.

Table 2
Currently approved antiretroviral drugs for children for the treatment of HIV-1 infection.

Drug name and dosage form	Age/weight recommendations for pediatric labeling
Nucleoside reverse transcriptase inhibitors (NRTIs)	
Combivir (lamivudine/zidovudine) Tablet	Pediatric patients who weigh greater than or equal to 30 kg
Emtriva (emtricitabine) capsule and solution	Birth to 18 years
Epivir (lamivudine) tablet and solution	3 months to 18 years
Epzicom (abacavir/lamivudine) tablet	No labeling for patients less than 18 years
Retrovir (zidovudine) capsule, syrup and tablet	6 weeks to 18 years and weighing at least 4 kg
Trizivir (abacavir/zidovudine/lamivudine) tablet	Adolescents (12–18 years) and weighing at least 40 kg
Truvada (tenofovir disoproxil fumarate/emtricitabine) tablet	No labeling for pediatric patients
Videx EC (enteric coated didanosine) capsule	6–18 years and weighing at least 20 kg
Videx (didanosine) oral solution	2 weeks to 18 years
Viread (tenofovir disoproxil fumarate) tablet	No labeling for pediatric patients
Zerit (stavudine) capsule and solution	Birth to 18 years
Ziagen (abacavir) tablet and solution	3 months to 18 years
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	
Intelence (etravirine) tablet	No labeling for pediatric patients
Rescriptor (delavirdine) tablet	No labeling for pediatric patients
Sustiva (efavirenz) capsule and tablet	At least 3 years and at least 10 kg
Viramune (nevirapine) tablet and suspension	15 days to 18 years
NRTI/NNRTI fixed-dose combination product	
Atripla tablet	No labeling for pediatric patients
Protease inhibitors (PIs)	
Aptivus (tipranavir) capsule and solution	2 to 18 years
Invirase (saquinavir mesylate) capsule and tablet	No labeling for pediatric patients
Kaletra (lopinavir/ritonavir) tablet and solution	2 weeks to 18 years
Lexiva (fosamprenavir) tablet and suspension	2 to 18 years
Norvir (ritonavir) capsule and solution	1 month to 18 years
Prezista (darunavir) tablet	6 to 18 years and weighing at least 20 kg
Reyataz (atazanavir sulfate) capsule	6 to 18 years and weighing at least 15 kg
Viracept (nelfinavir mesylate) tablet and powder	2 to 18 years and weighing at least 9 kg
Fusion inhibitors	
Fuzeon (Enfuvirtide) injectable	6 to 18 years and weighing at least 11 kg
Entry inhibitors	
Selzentry (maraviroc) tablet	No labeling for pediatric patients
HIV integrase strand transfer inhibitors	
Isentress (raltegravir) tablet	No labeling for pediatric patients

Obtaining the necessary nonclinical and clinical safety data to allow pregnant women to continue in trials is important for interpretation of trial results. High rates of discontinuations and lost-to-follow-up will impact the ability to conclude if a product is efficacious. Lack of data in the pregnant population at the time of approval of a microbicide may result in more harm because clinicians and users may opt to utilize a product with undefined risks in the post-approval period. Women may also avoid use of an efficacious product because the effects on pregnancy are not described.

Similar challenges exist for developing oral products for HIV prevention (pre-exposure prophylaxis (PrEP)). One key issue for PrEP trials is the ability to extrapolate data from one risk group to another. For example if a product is found efficacious in heterosexual women at high risk for HIV acquisition, do these results also apply to men who have sex with men or intravenous drug users? Currently PrEP trials are placebo-controlled trials, but if any trial shows efficacy in a given population, the results could likely affect ongoing placebo-controlled trials in other populations. The risk/benefit assessment must be carefully considered along with available biologic and scientific data prior to considering a product "standard-of-care" for all high-risk groups. An oral or topical microbicide product holds promise for reducing HIV transmission. The challenge is to understand the risk/benefit profile and social/behavioral implications prior to widespread availability of a product. These challenges and others are continually discussed among researchers, community activists, funders and government agencies.

7. Conclusion

Despite the medical advances and research progress of the past 20 years, a cure for HIV-1 infection remains elusive. HIV/AIDS is still a serious infection and while difficult and expensive to treat, it has become a chronic illness for most people rather than a fatal disease.

The challenge that continues to confront all of us is the ability to predict the future needs of the evolving HIV-1 treatment-experienced population. Physicians, patients, investigators and drug regulators face difficult decisions on whether to delay or to immediately use new therapies. Should patients enroll into a clinical trial with one new investigational agent or wait for the availability of two or more new drugs? How might new therapies affect future treatment options? The timing of new drugs and the sequencing of new drugs are critical decisions in the long term management of such patients and clinical trial development.

Regulators continually provide a risk/benefit assessment to try to balance safety and efficacy concerns with providing new ARV therapies as quickly as possible. The attitudes and opinions of scientists and physicians working in a regulatory agency should mirror the concerns of the public, patients, activists and pharmaceutical companies, so the decisions reached provide a path forward for the development of new ARVs. A spirit of cooperation maintained by regulators and other negotiating parties, unifying to move forward towards a common goal of helping patients has been a major strength in ARV drug development and holds promise to address future and existing challenges.

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