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Drug Resistance in HIV-1

Daniel R. Kuritzkes, M.D.

Division of Infectious Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, MA USA

Abstract

Purpose of the review—Changing antiretroviral regimens and the introduction of new antiretroviral drugs have altered drug resistance patterns in resistance human immunodeficiency virus type 1 (HIV-1). This review summarizes recent information on antiretroviral drug resistance.

Recent findings—As tenofovir and abacavir have replaced zidovudine and stavudine in antiretroviral regimens, thymidine analog resistance mutations have become less common in patients failing antiretroviral therapy in developed countries. Similarly, the near universal use of ritonavir-boosted protease inhibitors (PI) in place of unboosted PIs has made the selection of PI resistance mutations uncommon in patients failing a first- or second-line PI regimen. The challenge of treating patients with multidrug-resistant HIV-1 has largely been addressed by the advent of newer PIs, second-generation non-nucleoside reverse transcriptase inhibitors and drugs in novel classes, including integrase inhibitors and CCR5 antagonists. Resistance to these newer agents can emerge, however, resulting in the appearance of novel drug resistance mutations in the HIV-1 polymerase, integrase and envelope genes.

Summary—New drugs make possible the effective treatment of multidrug-resistant HIV-1, but the activity of these drugs may be limited by the appearance of novel drug resistance mutations.

Introduction

Changing antiretroviral regimens, and the introduction of new drugs and new drug classes into clinical practice have resulted in new patterns of drug resistance. Key findings from recent papers and conferences are summarized in this review.

Changing patterns of HIV drug resistance

If the first decade of antiretroviral therapy (ART) was dominated by the use of single- and dual-drug regimens, the second decade was dominated by the search for regimens effective against HIV-1 that had developed resistance to those initial regimens. The widespread use of thymidine analogs such as zidovudine (ZDV) and stavudine (d4T) led to the common appearance of thymidine analog resistance mutations (TAMs) [1]. The accumulation of TAMs selected by ZDV and/or d4T resulted in cross-resistance to all members of the nucleoside reverse transcriptase inhibitor (NRTI) class [2]. The addition of protease inhibitors (PI) or non-nucleoside reverse transcriptase inhibitors (NNRTI) to failing

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Address correspondence to: Daniel R. Kuritzkes, M.D., Division of Infectious Diseases, Brigham and Women's Hospital, 65 Landsdowne St, Rm 449, Cambridge, MA 02139, Tel: 617 768 8373, Fax: 617 768 8738, dkuritzkes@partners.org.

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regimens in the setting of extensive TAMs produced only transient clinical benefit and resulted in resistance to these newer drugs. In this setting, triple-class resistance (i.e., resistance to NRTIs, NNRTIs and PIs) became commonplace, creating significant therapeutic challenges [3].

The last decade has seen a significant shift in the patterns of HIV-1 drug resistance. Efavirenz (EFV) administered as first-line ART together with 2 NRTI resulted in higher rates of virologic suppression and hence lower overall rates of drug resistance. The replacement of ZDV, d4T and didanosine (ddI) with drugs such as tenofovir (TDF) and abacavir (ABC) improved the overall tolerability of first-line regimens, contributing to increasing rates of viral suppression that in clinical trials approached 90% after two years of follow-up [4,5,6*]. As a consequence, the most common resistance mutations at the time of virologic failure are now those that confer resistance to EFV or nevirapine (NVP) along with resistance to lamivudine (3TC) or emtricitabine (FTC); resistance to TDF or ABC is relatively uncommon [6*].

Similarly, ritonavir-boosted PIs showed superiority over unboosted PI regimens. A notable feature of boosted PI regimens has been the virtual absence of PI resistance at the time of treatment failure, attributed to the high genetic and pharmacologic barrier of these regimens [6–9]. Resistance to the NRTI component of an initial boosted-PI regimen is also less common than with unboosted PI regimens [7] or with NNRTI-based regimens [10]. Although PI resistance can emerge after prolonged exposure to a boosted PI in the setting of incomplete viral suppression [11,12*], it remains relatively rare.

Transmitted drug resistance

One consequence of a high prevalence of drug-resistant HIV-1 is the risk that such viruses will be transmitted. A study conducted at sentinel HIV-1 testing sites by the US Centers for Disease Control and Prevention (CDC) found the overall prevalence of antiretroviral drug resistance mutations in samples from persons newly diagnosed with HIV-1 infection during 1997–2001 was 8.3% [13]. Resistance to NRTIs was the most common (6.4%); resistance to the NNRTIs and PIs was substantially less common (1.7% and 1.9%, respectively), and resistance to drugs from 2 or more classes was present in only 1.3% of samples. An updated study covering the period from 2001 to 2006 found that the prevalence of transmitted drug resistance had increased to 14.6% [14**]. Notably, the pattern of resistance had shifted: NNRTI resistance was now most common (7.8%), followed by resistance to the NRTIs (5.6%) and PIs 4.5%); the prevalence of triple-class resistance remained low (0.7%). By contrast, transmission of drug-resistant HIV-1 appears to be stabilizing in Europe, with an overall prevalence of 8.4% [15*].

Treatment of drug-resistant HIV-1

Advances over the last five years have transformed the treatment of patients with multidrug-resistant HIV-1. This transformation was fueled by the introduction of PIs with increased activity against many PI-resistant viruses (notably tipranavir and darunavir) [16,17], along with the second-generation NNRTI etravirine (ETV) [18,19] and drugs in novel classes, including the integrase inhibitor raltegravir (RAL) [20] and the CCR5 antagonist maraviroc (MVC) [21]. As a result, it is now possible to prescribe fully active ART regimens and achieve full virologic suppression in most patients with highly drug-resistant HIV-1 [22*, 23*]. Despite their effectiveness, resistance to these drugs can develop. The following sections review recent data on resistance to the newest drugs (ETV, RAL and MVC); resistance to rilpivirine (RPV), a second-generation NNRTI recently approved for initial antiretroviral therapy, is also discussed.

Resistance to second-generation NNRTIs

Etravirine (formerly TMC125) and RPV (formerly TMC278) (Figure 1) are potent second-generation NNRTIs that retain activity against EFV-resistant viruses carrying the K103N mutation in HIV-1 reverse transcriptase (RT) [24,25*]. The E138K mutation, which emerges both in vitro and in vivo, confers resistance to ETV and RPV [25*,26*,27*]. In vitro selection using clinical isolates from several different HIV-1 subtypes found that the E138K mutation was usually the first mutation to emerge in all isolates [26*]. A number of amino acid substitutions at RT position 138, including E138K, were identified in HIV-1 after failure of ETV in the phase 3 trials [27*]. Molecular modeling studies suggest that the E138K mutation disrupts a salt bridge between Lys¹⁰¹ and Glu¹³⁸, expanding the NNRTI binding pocket and reducing affinity for the RPV and ETV [28]. It has been proposed that the M184I mutation reduces susceptibility to these drugs by further distorting the NNRTI binding pocket [28].

A multivariate analysis of data from the phase 3 clinical trials of ETV in ART-experienced patients identified 17 NNRTI resistance mutations that influence response to this drug [29**]. The presence of increasing numbers of NNRTI resistance mutations at study entry (selected by past exposure to EFV or NVP) was associated with decreasing virologic response to an ETV-containing regimen. A scoring has been devised in which each mutation is given a particular weight; the overall effect of the mutations on response to ETV is determined by summing the individual mutation weights. Scores of 0.0–2.0 are associated with a high response to ETV (74% of subjects achieved a virus load <50 copies/mL); scores of 2.5–3.5 are associated with intermediate responses (52% <50 copies/mL); and scores of 4.0 or more are associated with reduced responses (~38%). Recent data suggest that mutations in region that connects the polymerase and RNaseH domains of RT (the “connection” domain) can increase resistance to NRTI and NNRTI (for a review see [30]). The contribution of mutations in the connection domain of RT to ETV susceptibility remains controversial [31*,32*]. Analyses performed with phenotypic data found that the proportion of patients responding to an ETV-containing regimen begins to diminish when the fold-increase in effective concentration (EC₅₀) of ETV as compared to wild-type exceeds 3.0; a fold-change of 13 or more is associated with an ETV response that is no different from placebo [29**].

Clinical trials of RPV in treatment-naïve patients show that HIV-1 carrying the E138K mutation emerged in approximately 60% of patients with virologic failure [33**,34]. In most cases, the E138K mutation was accompanied by the M184I mutation, which confers resistance to 3TC and FTC (in addition to RPV, patients received either 3TC or FTC together with another NRTI). Although M184I may emerge early on, typically it is rapidly replaced by M184V [35,36]. In vitro studies with site-directed mutants carrying various combinations of these mutations showed that the E138K, M184I and M184V mutations each reduced replication capacity and viral fitness, but that the combined presence of E138K plus M184I or V restored replication capacity to wild-type levels [37*]. Biochemical analysis of purified RT noted improved processivity of the E138K/M184I(V) mutant enzymes as compared to wild-type or M184I(V) RT [38*]. The E138K/M184I mutant showed a fitness advantage over the E138K/M184V mutant; this difference was accentuated in the presence of ETV and 3TC [37*].

Resistance to integrase strand-transfer inhibitors

Integrase (IN) catalyzes the covalent insertion of the double-stranded DNA product of HIV-1 reverse transcription into the host chromosome. Together with other viral and cellular proteins, IN binds to specific sequences of the HIV-1 cDNA to form the pre-integration

complex. The IN cleaves 2 nucleotides from the 3'-end of each strand of the cDNA molecule, and ligates the 5'-ends of the cDNA to the chromosomal DNA in a process known as strand transfer. Compounds that block strand transfer are known as integrase strand transfer inhibitors (INSTI).

Raltegravir

Raltegravir (Figure 2) is the first INSTI approved for the treatment of HIV-1 infection. Data from clinical trials show that RAL resistance involves IN mutations Y143C(R), Q148H(R) (K) or N155H, together with associated secondary mutations that result in higher levels of resistance [39,40*,41*,42*] (for a review see [43**]). These mutations are located within the catalytic core domain of IN, and reduce viral replication capacity [44*]. The N155H mutant generally emerges first, and is eventually replaced by Q148H mutants, usually in combination with G140S [45*,46]. Transmission of a RAL-resistant virus carrying the Q148H/G140S mutations has been documented [47*].

Deep sequencing analysis suggests that the transition from N155H to Q148H/G140S occurs by de novo mutation and/or recombination, but that the N155H and Q148H mutations are not found on the same viral genome, presumably due to the low fitness of the double mutant [48*]. In vitro growth competition studies show that in the presence of RAL, the N155H mutant is fitter than the Q148H mutant, but the Q148H/G140S double mutant is fitter than single mutants or the N155H/E92Q double mutant [49*]. These results are consistent with those of another study in which the relative infectivity of various raltegravir-resistant mutants was compared to that of wild-type virus at different drug concentrations [50*], and help explain the ordered appearance of RAL resistance mutations.

The Y143C(R) mutation is observed less frequently than the Q148H or N155H mutations, and may be accompanied by T97A as a secondary mutation. The T97A mutation substantially increases the level of RAL resistance and restores integrase catalytic activity, which is reduced by the Y143C(R) mutation [51]. In vitro data suggest that the Y143R mutant remains susceptible to elvitegravir, but the clinical significance of this finding has not been confirmed [52].

Recent data suggest that RAL resistance may emerge more commonly in patients with high baseline virus loads. Raltegravir resistance mutations were found in virus from 11 of 38 patients with virologic failure in a randomized trial of once- versus twice-daily RAL [53*]; baseline plasma HIV-1 RNA levels were above 100,000 copies/mL in 9 of these 11 patients. Presence of RAL resistance mutations at time of virologic failure was also associated with high baseline plasma HIV-1 RNA in pilot studies of RAL plus atazanavir [54] or RAL plus ritonavir-boosted darunavir [55*]. A possible explanation for the apparent association between high baseline plasma HIV-1 RNA levels and risk of virologic failure with RAL resistance could be a greater absolute number low-frequency RAL-resistance mutations in the virus populations of patients with high virus loads [56**].

Elvitegravir

Elvitegravir (Figure 2) is an investigational integrase inhibitor currently being studied in phase 3 clinical trials. Primary resistance mutations, based on results of in vitro selection experiments, include the Q143R, E92Q and T66I mutations [57]. The E92Q has been reported in virus from patients with virologic failure while receiving elvitegravir [58]. The N155H and Q148H mutations selected by RAL confer cross-resistance to elvitegravir, but the E92Q and T66I mutations do not confer significant cross-resistance to RAL [43**]. Better characterization of mutations selected by elvitegravir awaits the results of ongoing phase 3 clinical trials.

Dolutegravir

Dolutegravir (Figure 2), another investigational integrase inhibitor in phase 3 clinical trials, has potent in vitro activity against many RAL-resistant viruses [59**]. Viruses carrying a mutation at IN position 148 along with secondary RAL resistance mutations show decreased susceptibility to dolutegravir [60]. This decreased susceptibility correlated with reduced antiviral activity in patients with HIV-1 carrying a 148 mutation plus one or more associated RAL resistance mutations (Eron et al., abstract 151LB, 18th Conference on Retroviruses and Opportunistic Infections, Boston, MA, February, 2011). Doubling the dose of dolutegravir from 50 mg once daily to 50 mg twice daily appeared to improve virologic responses in such patients. Ongoing phase 3 clinical trials will help define more precisely the efficacy of dolutegravir against RAL-resistant viruses.

CCR5 antagonists

Entry of HIV-1 into target cells requires the sequential interaction of the viral envelope glycoprotein with two receptors—CD4, the primary receptor, and either CCR5 or CXCR4, which serve as co-receptors. Early after infection with HIV-1, most patients harbor virus that uses CCR5 exclusively as co-receptor (termed R5 viruses). Later in infection, CXCR4-using (X4) variants can be found in many patients (for a review see [61]). Small-molecule CCR5 antagonists with anti-HIV activity are allosteric noncompetitive antagonists of HIV-1 entry. Binding of these drugs to CCR5 leads to a conformational change of the chemokine receptor that prevents its interaction with the HIV envelope glycoprotein. Maraviroc (Figure 3) is the first CCR5 antagonist approved for clinical use. The anti-HIV activity of maraviroc and other CCR5 antagonists is limited to blocking entry of R5 viruses.

Emergence of CXCR4-using viruses appears to be the most common viral adaptation associated with virologic failure of maraviroc and other CCR5 antagonists [62–64]. These CXCR4-using viruses emerge from pre-existing minority variants that are not detected by conventional assays [65]. Because studies from the pre-ART era showed that emergence of CXCR4-using virus in untreated patients is associated with an increased risk of disease progression and death [66], there was concern that selection of such viruses by CCR5 antagonists would accelerate disease progression. This concern appears to be unwarranted—emergence of CXCR4-using viruses in patients treated with these antagonists has not been associated with adverse clinical outcomes [67]. Upon discontinuation of the antagonist, the virus population reverts to CCR5 use, suggesting that CXCR4-using variants selected under drug pressure are less fit than R5 virus [68].

Less commonly, HIV-1 can adapt to use the drug-bound form of CCR5. Emergence of such variants has been documented following in vitro passage in the presence of maraviroc and other CCR5 antagonists, and in clinical trials of these drugs (for a review, see [69]). Adaptation to use of drug-bound CCR5 usually is mediated by substitutions in both stems of the V3 loop of gp120 [70,71,72*,73], although at least one example of mutations in the fusion domain of gp41 has been noted [74**].

In contrast to resistance to drugs in other classes, no group of mutations has been identified that is shared consistently among CCR5 antagonist-resistant viruses. The effects of particular mutations associated with resistance in one isolate may be quite different when introduced into a heterologous *env* backbone [75]. Some studies suggest that CCR5 antagonist-resistant viruses are more dependent on interactions with the N-terminus of CCR5 and less dependent on interactions with the second extracellular loop of the receptor, but not all resistant viruses share these properties [76*,77*]. As only a handful of HIV-1 clinical isolates resistant to CCR5 antagonists have been characterized to date, much

remains to be learned about the genotypic determinants of resistance to this class of drugs and the biochemical mechanisms involved.

Conclusions

Substantial progress has been made in understanding the biology of HIV-1 drug resistance over the last 25 years. Recently approved antiretroviral drugs allow successful treatment of most patients with highly drug-resistant HIV-1 infection, but these advances are limited to countries with the resources to pay for newer drugs and viral diagnostics. Continued efforts to develop new drugs are also needed, given the seemingly endless capacity of HIV-1 to adapt to each new class of antiretroviral drugs introduced into clinical practice.

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Highlights

- Patterns of HIV-1 drug resistance have changed
- New drugs allow treatment of most highly resistant isolates.
- Novel patterns of resistance have been described for these newer drugs.

Figure 1.
Molecular structure of etravirine and rilpivirine, 2nd-generation non-nucleoside RT inhibitors.

Figure 2.
Molecular structure of raltegravir, elvitegravir and dolutegravir, integrase strand-transfer inhibitors.

Maraviroc

Figure 3.
Molecular structure of maraviroc, a CCR5 antagonist.