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SUPPLEMENT ARTICLE

Human Immunodeficiency Virus Type 1 Drug Resistance Mutations Update

Robert W. Shafer

Division of Infectious Diseases, Department of Medicine, Stanford University School of Medicine, California

As treatment options coalesce around a smaller number of antiretroviral drugs (ARVs), data are emerging on the drug resistance mutations (DRMs) selected by the most widely used ARVs and on the impact of these DRMs on ARV susceptibility and virological response to first- and later-line treatment regimens. Recent studies have described the DRMs that emerge in patients receiving tenofovir prodrugs, the nonnucleoside reverse transcriptase inhibitors efavirenz and rilpivirine, ritonavir-boosted lopinavir, and the integrase inhibitors raltegravir and elvitegravir. Several small studies have described DRMs that emerge in patients receiving dolutegravir.

Keywords. human immunodeficiency virus type 1; antiviral drug therapy; reverse transcriptase; protease; integrase.

The most widely used antiretroviral drugs (ARVs) include (*i*) 6 nucleoside reverse transcriptase inhibitors (NRTIs): the cytosine analogues lamivudine (3TC) and emtricitabine (FTC), the tenofovir prodrugs tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF), abacavir (ABC), and zidovudine (ZDV); (*ii*) 3 nonnucleoside reverse transcriptase inhibitors (NNRTIs): efavirenz (EFV), rilpivirine (RPV), and etravirine (ETR); (*iii*) 3 pharmacologically boosted protease inhibitors (PIs): ritonavir-boosted lopinavir (bLPV) and ritonavir- or cobicistat-boosted atazanavir (bATV) and darunavir (bDRV); and (*iv*) 3 integrase strand transfer inhibitors (INSTIs): raltegravir (RAL), elvitegravir (EVG), and dolutegravir (DTG). This review highlights recently published data on NRTI, NNRTI, PI, and INSTI-associated DRMs. For an update on ARVs and DRMs not covered in this review, the reader is referred to the 2017 update of the International Antiviral Society–USA mutation list [1] and the DRM Comments and Notes sections of the Stanford HIV Drug Resistance Database [2]. For data on the genetic mechanisms of resistance to the entry inhibitors enfuvirtide and maraviroc, the reader is referred to other recent human immunodeficiency virus (HIV) drug resistance reviews [3, 4].

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

There have been several recent large studies of the DRMs occurring in patients with virological failure (VF) on first-line TDF-containing regimens, particularly in low- and middle-income countries [5, 6]. In patients without preexisting thymidine analogue mutations (TAMs), there are 2 main nonoverlapping pathways to TDF resistance following VF: the development of K65R, which occurs in about 40% of patients, and K70E/Q, which occurs in about 10% of patients [5]. Although K65R causes a greater reduction in TDF susceptibility than K70E, it is associated with a greater reduction in replication capacity [7–9]. K70E and K65R rarely occur in combination because viruses with both mutations have a >95% reduction in replication capacity [7].

Several additional TDF-selected DRMs have been reported in patients with VF on a first-line TDF-containing regimen including S68G/N/D (20% of patients), Y115F (12%), A62V (10%), L74I (6%), K70N/T/G (3.2%), K65N (0.7%), and T69 deletions (0.3%) [5]. A62V and S68G have been reported to increase the fitness of viruses containing K65R [10], whereas Y115F has been reported to reduce TDF susceptibility [9, 11].

TDF-selected DRMs surprisingly cause just moderate reductions in TDF susceptibility—usually ≤2.0 fold, particularly when they occur in combination with the cytosine-analogue DRMs M184V/I (which increase TDF susceptibility) [9, 12]. In contrast, the highest levels of TDF resistance are conferred by DRMs selected by older NRTIs. The combinations of the 3 type 1 TAMs, M41L + L210W + T215Y, of TAMs + T69 insertions, and of Q151M + K65R usually reduce TDF susceptibility >5.0-fold [9, 12].

Most TDF-selected DRMs including K65R/N, Y115F, L74I, and K70E/Q/N/T/G confer ABC cross-resistance [8, 9, 11, 13]. K65R reduces 3TC and FTC susceptibility, but to an extent much less than M184V/I [9, 12]. None of the TDF-selected mutations have been reported to reduce ZDV susceptibility, making ZDV an option for treating viruses with TDF resistance but without TAMs. The prodrug TAF selects for many of the same DRMs selected by TDF [14–16]. The phenotypic effects of these DRMs on TDF and TAF are similar [14, 15].

Correspondence: R. W. Shafer, MD, Stanford University, Stanford, CA (rshafer@stanford.edu).

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NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

The most common major NNRTI mutations are L100I, K101E/P, K103N/S, V106A/M, Y181C/I/V, Y188C/H/L, G190A/S/E, and M230L. With the exception of Y181C/I/V, each confers intermediate- or high-level reductions in susceptibility to EFV [17]. L100I, K101E/P, Y181C/I/V, G190E, and M230L reduce susceptibility to ETR and RPV [17–20], and Y188L reduces susceptibility to RPV but not ETR [18, 20].

The approval of RPV led to the recognition of several novel NNRTI-associated DRMs including E138A/K/Q/G/R, which are among the most common RPV-selected DRMs [21]. Combined data from several studies have shown that E138A/G/K/Q confer minimal but discernable reductions in susceptibility to RPV and ETR, but not EFV [17, 18, 22–25]. Whereas E138K/G/Q/R rarely occur in the absence of NNRTI exposure, E138A occurs in 1%–6% of viruses from untreated patients depending on subtype, with the highest levels observed in subtypes A and C [24, 26]. Subtypes A and C viruses may also be predisposed to develop E138G/Q during EFV therapy [27, 28].

Several recent large studies have described the spectrum of EFV-selected DRMs in different HIV-1 subtypes, confirming the increased frequency of V106M in subtype C viruses [5, 28, 29]. In addition, a recent study of patients from the former Soviet Union with VF on an EFV-containing regimen reported that subtype A viruses from this region are uniquely predisposed to developing G190S [30].

PROTEASE INHIBITORS

Approximately 5%–10% of patients with VF while receiving bLPV and bATV, and 2% of patients with VF while receiving bDRV, as an initial boosted PI develop PI resistance mutations [31–36]. In patients receiving bLPV who develop PI resistance mutations, the following have each been reported in >5% of patients: V32I, M46I/L, I47A/V, I50V, I54V, L76V, V82A, I84V, and L90M [31, 37–40]. These viruses are predicted to often have low-level and occasionally intermediate cross-resistance to DRV [31, 37–40]. Although bATV is increasingly used for second-line therapy, it is not yet known whether the spectrum of bATV-selected mutations extends beyond the originally identified bATV-selected mutations, I50L and N88S.

Two explanations have been proposed for the infrequency of PI resistance protease mutations following VF on an initial boosted PI–containing regimen. The first is that PI resistance protease DRMs develop only in viruses exposed to a narrow window of suboptimal drug concentrations that both exert selective pressure and allow virus replication [41]. This explanation is supported by the observation that most patients with VF on an initial PI-containing regimen without PI resistance protease mutations achieve virological resuppression with improved adherence alone [42–44].

The second explanation is that mutations outside of protease might reduce PI susceptibility even in the absence of PI resistance protease mutations. Although many studies have shown that *gag* cleavage and non–cleavage site mutations influence PI susceptibility (reviewed in [45]), it has been difficult to identify specific *gag* mutations consistently associated with VF on a boosted PI–containing regimen [46]. Although 1 study reported that pseudotyped viruses containing the cytoplasmic domain of *gp41* from PI-resistant strains have reduced PI susceptibility in the absence of PI resistance protease mutations [47], there is no evidence yet of mutations in this region reducing susceptibility in clinical virus isolates.

INTEGRASE STRAND TRANSFER INHIBITORS

Many RAL-selected DRMs have been identified because, when first approved, RAL was often used for salvage therapy without other active ARVs. Three main overlapping mutational pathways to RAL resistance were identified: (*i*) Q148H/R/K ± G140A/S/C ± E138A/K/T; (*ii*) N155H ± E92Q; and (*iii*) Y143C/R [48]. The first 2 pathways also occur in patients receiving EVG and confer EVG resistance. Although Y143C/R are not selected by EVG, DRMs at this position reduce EVG susceptibility when they occur in combination with additional accessory DRMs [49]. There are also several DRMs that occur primarily in viruses from patients receiving EVG including T66A/I/K, P145S, and S147G [48, 50].

Most data on the DRMs associated with DTG resistance are from RAL-experienced patients who received DTG salvage therapy in the VIKING trials [51, 52]. In these trials, patients whose viruses had a baseline Q148 mutation in combination with an E138 and/or G140 mutation were at increased risk of VF. Depending on the particular combination of DRMs at these positions, DTG susceptibility may be reduced between 2-fold and 10-fold. The Q148 pathway appears to be the main springboard for the development of high-level DTG resistance because the addition of 1 or 2 of several other INSTI-associated DRMs including polymorphic accessory DRMs such as L74I/M and T97A can result in much greater reductions in DTG susceptibility [52].

There has been a gradually increasing number of reports of VF and emergent INSTI resistance in ARV-experienced INSTI-naive patients receiving a DTG-containing regimen [50, 53] and in virologically suppressed patients receiving DTG monotherapy [54, 55]. R263K has been reported in 4 patients in the first scenario [50, 53]. Whereas, Q148H/R (3 patients), N155H (3 patients), G118R (2 patients), S230R (2 patients), and R263K (1 patient) have been reported following VF during DTG monotherapy [54, 56].

R263K is an uncommon nonpolymorphic mutation selected in vitro by DTG [57]. Its clinical significance is not well understood because it causes a minimal <2-fold reduction in DTG susceptibility, is associated with reduced viral replication, and rarely occurs in combination with other DTG resistance mutations [52, 57, 58]. G118R is an even less common mutation that is also selected in vitro by DTG [55]. Like R263K, it appears to have only

a minimal effect on DTG susceptibility [59, 60] and has not been reported in combination with other INSTI resistance mutations.

There is a high correlation between the phenotypic effects of INSTI DRMs on DTG and the investigational INSTI bictegravir [61]. Preliminary in vitro data, however, suggest that the long-acting investigational INSTI cabotegravir may have a lower genetic barrier to resistance than DTG [62].

CONCLUSIONS

An extensive amount of data have recently been published on the DRMs arising in patients receiving first-line TDF and EFV-containing regimens and second-line bLPV-containing regimens. An increased recognition of the DRMs selected by RAL, EVG, and RPV is also emerging. Insufficient data, however, are available on the DRMs selected by bATV and DTG and the genotypic predictors of response to second- and third-line therapy with these ARVs and bDRV.

Notes

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