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Antiretroviral medication adherence and the development of class-specific antiretroviral resistance

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Abstract

Objective: To assess the association between antiretroviral adherence and the development of class-specific antiretroviral medication resistance.

Design and methods: Literature and conference abstract review of studies assessing the association between adherence to antiretroviral therapy and the development of antiretroviral medication resistance.

Results: Factors that determine class-specific adherence–resistance relationships include antiretroviral regimen potency, viral fitness or more specifically the interplay between the fold-change in resistance and fold-change in fitness caused by drug resistance mutations, and the genetic barrier to antiretroviral resistance. During multidrug therapy, differential drug exposure increases the likelihood of developing resistance. In addition, antiretroviral medications with higher potency and higher genetic barriers to resistance decrease the incidence of resistance for companion antiretroviral medications at all adherence levels.

Conclusion: Knowledge of class-specific adherence–resistance relationships may help clinicians and patients tailor therapy to match individual patterns of adherence in order to minimize the development of resistance at failure. In addition, this information may guide the selection of optimal drug combinations and regimen sequences to improve the durability of antiretroviral therapy.

Keywords

adherence; antiretroviral resistance; antiretroviral therapy; genetic barrier to resistance; HIV; potency; replication capacity

Introduction

In the era of potent combination antiretroviral chemotherapy, HIV-1 infection is a treatable chronic disease [1]. The median life expectancy of persons entering care with HIV-1 infection

and access to antiretroviral therapy is 24–39 years [2,3]. Nevertheless, the effectiveness of antiretroviral therapy can be limited by lack of access to therapy, poor adherence, intolerance, or antiretroviral resistance. Although resistance may be transmitted, most resistance arises *de novo* during viral replication. The enzyme responsible for viral replication, HIV-1 reverse transcriptase, is error prone with every possible point mutation in the HIV-1 genome occurring 10,000–100,000 times daily in untreated individuals [4-7].

Some mutations confer resistance to antiretroviral medications. Resistant viruses establish a stable, low frequency population but wild-type HIV-1 remains predominant because it generally replicates more efficiently [6]. Under certain circumstances, mutations confer a survival advantage. Drug resistance mutations proliferate during nonsuppressive antiretroviral therapy, which is usually the result of inadequate drug exposure [8]. As poor adherence is the major determinant of inadequate drug exposure, antiretroviral adherence is critically linked to the development of antiretroviral resistance.

The propensity for resistance differs for different drug classes and, in some cases, for individual medications within a drug class. For example, failure of nonnucleoside reverse transcriptase inhibitor (NNRTI)-based initial therapy is commonly associated with dual-class resistance to NNRTIs and nucleoside analogue reverse transcriptase inhibitors (NRTIs) [9]. In contrast, failure of boosted protease inhibitor-based initial therapy is rarely associated with major protease mutations, though reverse transcriptase mutations occur commonly, particularly to deoxycytidine analogue NRTIs (lamivudine and emtricitabine) [10]. These drug-specific and class-specific differences can be explained through a detailed understanding of the association between adherence and the development of resistance.

The main factors influencing class-specific adherence–resistance relationships include antiretroviral potency, the fitness of HIV-1 possessing antiretroviral resistance mutations, and the genetic barrier to antiretroviral resistance for antiretroviral agents. We begin by describing the effect of these factors on adherence–resistance relationships. Then, we examine the evidence for the interrelationship of these factors within individual drug classes. Following this, we discuss the application of single-class adherence–resistance relationships to multidrug antiretroviral therapy. This discussion includes two additional factors that influence adherence–resistance relationships; differential drug exposure during treatment and the attributes of the other components of multidrug antiretroviral therapy. Finally, we suggest ways in which this information may influence clinical practice.

Antiretroviral potency

Antiretroviral potency can be estimated by the slope of the first phase of viral decay after initiation of an antiretroviral agent [11]. Antiretroviral regimen potency can be defined as the likelihood that a given antiretroviral regimen will suppress HIV-1 viremia below the limits of standard assay detection for prolonged periods of time. At very low viral loads, rates of viral replication are extremely low and circulating virus largely emanates from latent reservoirs of infected cells [12]. In this setting, the chance that resistance to a single component, or multiple components, of an antiretroviral regimen will arise *de novo* is low – fewer replication cycles give fewer opportunities for individual point mutations to occur [13].

Differences in antiretroviral regimen potency can be illustrated by contrasting the effects of nonadherence for nonboosted versus NNRTI-based and boosted protease inhibitor-based regimens. Initial studies assessing the association between adherence and regimen potency on nonboosted protease inhibitor-based combination therapy led to the view that more than 95% adherence was required for the best chance of suppressing viremia below the limits of detection [14-16]. Modern, more potent initial regimens such as NNRTI-based or boosted protease inhibitor-based combination therapy achieve virological success rates of 80–90% with levels

of adherence as low as 50–60% in some studies [17–19]. Thus, NNRTI and boosted protease inhibitor-based antiretroviral regimens are more potent than nonboosted protease inhibitor-based regimens, making the development of resistance at moderate (60–85%) to high (>85%) levels of adherence less likely on NNRTI-based or boosted protease inhibitor-based therapy.

The degree of resistance to an antiretroviral drug is determined by the fold-change in resistance – individual mutations lead to different levels of resistance. High-level resistance can occur with a single mutation –as with lamivudine, emtricitabine, or first-generation NNRTIs – or may require multiple mutations, as with most protease inhibitors and nondeoxycytidine analogue NRTIs [20]. A highly resistant virus has almost no impediment to replication in the presence of medications to which it is resistant; the fold-change in resistance is high. Conversely, a single-protease mutation confers low-level resistance. Thus, a viral strain having such a mutation will continue to be suppressed, at least to some degree, in the presence of a protease inhibitor; the fold-change in resistance is low. This concept will become more important when we discuss the determinants of circulating viral populations at low-to-moderate adherence levels.

Replication capacity and fitness

Replication capacity refers to the ability of HIV-1 to replicate *in vitro* under ideal circumstances. Fitness is similar except that it refers to the relative ability of a viral strain (compared with wild-type) to replicate in the presence of antiretroviral medication [21]. The relationship between fitness and circulating viral populations is defined by three factors: drug exposure and the ability of wild-type and resistant HIV-1 to replicate at that level of drug exposure [22]. Replication capacity and fitness exert their effect on adherence–resistance relationships at low-to-moderate levels of adherence in which viral replication occurs in the presence of circulating drug.

The relationship between single-drug exposure and the fitness of resistant versus wild-type HIV-1 has been explored using an in-vitro model [23]. Figure 1 shows in-vitro fitness curves generated using phenotypically defined NNRTI or protease inhibitor-resistant virus [23]. In Fig. 1a, as the concentration of nevirapine is increased (X-axis), wild-type HIV-1 replicates better than NNRTI-resistant HIV-1 (resistance/reference ratio <1, Y-axis) until the concentration of nevirapine reaches approximately 0.09mg/l, corresponding to an adherence level of about 2% (inset, Fig. 1a). At higher nevirapine concentrations, resistant virus replicates better than wild-type virus. Figure 1b shows the fitness curve for protease inhibitor-resistant compared with wild-type HIV-1 in the presence of nelfinavir [23]. Here drug-resistant virus does not gain a replicative advantage over wild-type HIV-1 until nelfinavir concentrations approach 0.7mg/l, suggesting that resistant virus will predominate at adherence levels greater than 85%.

These in-vitro data suggest that, when fitness is not impaired by resistance mutations, viremic patients will tend to have resistant virus circulating, outcompeting wild-type HIV-1 at just about all clinically relevant levels of drug exposure. The NNRTI class of antiretroviral medications fits this profile because resistance-conferring point mutations affect reverse transcriptase outside the enzymatic active site and are less likely to impact replication capacity. NNRTI-resistant virus usually has a low fold-change in fitness [8]. On the contrary, NRTIs and protease inhibitors usually have a high fold-change in fitness, and resistance-conferring mutations typically impact the enzymatic active sites.

The level of adherence at which the transition to wild-type HIV-1 occurs depends on the fold-change in resistance (the decreased ability of drug to suppress mutated HIV-1) and the fold-change in fitness (the decreased ability of resistant HIV-1 to replicate compared with wild-type HIV-1). These factors have opposing influences on the level of adherence at which the

transition from resistant to wild-type HIV-1 occurs. If the fold-change in resistance is high, as with NNRTIs, mutated virus has a competitive advantage because any amount of drug will suppress wild-type HIV-1, at least to some extent. If the fold-change in fitness is high, as with protease inhibitors, wild-type HIV-1 has a competitive advantage because of the impaired ability of mutated HIV-1 to replicate.

Genetic barrier to antiretroviral resistance

The genetic barrier to antiretroviral resistance can be defined as the number of genetic mutations required to cause antiretroviral drug resistance [24]. Low-barrier antiretroviral medications are those that require a single-point mutation for high-level resistance. These include the NRTI deoxycytidine analogues lamivudine and emtricitabine, first-generation NNRTIs like efavirenz and nevirapine, the fusion inhibitor enfuvirtide, and the protease inhibitor nelfinavir. Moderate-barrier antiretroviral medications require several mutations for resistance to develop. These include most nondeoxycytidine NRTI medications such as the thymidine analogues, didanosine, abacavir, and tenofovir, most nonboosted protease inhibitors, and some boosted protease inhibitors. High-barrier antiretroviral medications require many mutations before resistance develops. The boosted protease inhibitors darunavir and tipranavir are in this category.

When multiple mutations are required for the development of resistance, they occur sequentially rather than simultaneously [25]. Thus, the genetic barrier to antiretroviral resistance influences the adherence–resistance relationship by affecting the rate of development of resistance during periods of viral replication; more mutations require more time. In cross-sectional analyses, the barrier to resistance will primarily affect the proportion of individuals with resistance to their antiretroviral medications – the lower the barrier to resistance, the more likely an individual on that medication with viral replication will have resistance. In longitudinal analyses, this will primarily affect the incidence of resistance mutations, with low-barrier medications developing resistance more rapidly.

Class-specific adherence–resistance relationships

Antiretroviral potency, viral fitness, and the genetic barrier to antiretroviral resistance shape class-specific adherence–resistance relationships (Table 1). The adherence–resistance relationship for nonboosted protease inhibitor-based regimens is reviewed first because it has been the most extensively studied, even though these regimens are not commonly used today. Following an examination of the existing evidence on single-class adherence–resistance relationships, we will synthesize this information by discussing adherence–resistance relationships during multidrug therapy.

Nonboosted protease inhibitors

An initial cross-sectional analysis determined that adherence to nonboosted protease inhibitor-based therapy was higher in individuals with protease mutations than in those without protease mutations [14]. Although initially this association appeared paradoxical, these findings were substantiated in subsequent cross-sectional studies that utilized different means of adherence and resistance assessment [14,26,27]. Other studies supported these findings but were more difficult to interpret because they assessed overall resistance rather than class-specific resistance [28,29].

Incident resistance describes new resistance mutations accumulating over time in individuals initiating antiretroviral therapy. Mathematical models and the first longitudinal analyses of the association between adherence and incident resistance verified that the greatest risk of protease inhibitor resistance occurs at moderate-to-high (but not perfect) levels of adherence [30–32].

Incident resistance declines modestly with perfect levels of adherence [32]. This relationship, however, reflects the experience of two populations – suppressed and viremic individuals. Because resistance arises in the setting of active viral replication, resistance testing can only be performed during viremia. Prevalent resistance describes resistance present in individuals at the time antiretroviral therapy fails. For nonboosted protease inhibitors, prevalent resistance increases as adherence increases (Fig. 2b Fig. 2, ratio of black to dark gray bars) [23,32].

In summary, moderate potency permits viral replication and the development of resistance in some individuals with moderate-to-high levels of adherence. Because protease mutations impair fitness, as adherence declines in viremic individuals, there is a transition from resistant virus to wild-type virus predominating in the circulation. This transition occurs at low-to-moderate levels of adherence because the fold-change in resistance is not high (there continues to be suppression of some mutant viruses at low levels of adherence) and the fold-change in fitness is moderate-to-high (allowing wild-type HIV-1 to outcompete resistant virus at lower adherence levels). Finally, because the genetic barrier to antiretroviral resistance is low-to-moderate, the incidence of resistance is high.

Boosted protease inhibitors

Protease mutations rarely develop during initial treatment with boosted protease inhibitor-based antiretroviral therapy [10,33]. In a prospective randomized trial including 292 individuals starting lopinavir/ritonavir-based therapy, none of 74 individuals with virological failure developed primary protease mutations over 108 weeks [32]. Secondary protease mutations occurred in 2% of individuals; the highest risk was among individuals with 85–90% adherence. Among viremic individuals, the risk of secondary protease mutations increased as adherence increased, similar to nonboosted protease inhibitors. A second study that assessed boosted protease inhibitor adherence–resistance relationships found resistance in less than 1% of individuals over 4 months of follow-up; the greatest risk was in individuals with 75–95% adherence [18].

The high potency of boosted protease inhibitor-based therapy makes resistance unlikely to develop at moderate-to-high adherence levels. The fitness cost of resistance makes the development of protease inhibitor resistance unlikely at low-to-moderate levels of adherence. The moderate-to-high genetic barrier to resistance makes the incidence of resistance low in viremic individuals, thus full resistance occurs only after prolonged periods of viremia. Thus, in individuals receiving boosted protease inhibitor-based initial antiretroviral therapy, the development of protease inhibitor resistance is uncommon at all adherence levels. The few individuals who develop protease inhibitor resistance on boosted protease inhibitors have an adherence–resistance relationship similar to nonboosted protease inhibitors for the reasons discussed above.

First-generation nonnucleoside reverse transcriptase inhibitors

Contrary to the adherence–resistance relationship for protease inhibitors, incident NNRTI resistance is more likely at lower levels of adherence [18,23,34]. Bangsberg *et al.* [23] showed that for every 10% increase in adherence, the odds of NNRTI resistance decreased by 25% (Fig. 2a). Maggiolo *et al.* [18] showed that, compared with individuals with more than 95% adherence, the risk of failing with NNRTI resistance was 3.5 times higher for individuals with 75–95% adherence and five times higher for individuals with less than 75% adherence. In an analysis of the Community Programs for Clinical Research on AIDS (CPCRA) Flexible Initial Retrovirus Suppression Trial (FIRST, [35]), the risk of initial failure with NNRTI resistance was 2.3 times higher for individuals with 80–99% adherence and 6.5 times higher for individuals with less than 80% adherence compared with individuals with 100% adherence [34].

In viremic individuals, prevalent NNRTI resistance is common at all adherence levels. In the study by Bangsberg *et al.* [23], 75–100% of viremic individuals in each adherence quartile developed NNRTI resistance (Fig. 2a). In the study by Maggiolo *et al.* [18], 63–100% of individuals in each adherence strata (<75, 75–95, and >95%) developed NNRTI resistance at failure. High rates of NNRTI resistance have also been reported in prospective clinical trials among individuals failing NNRTI-containing antiretroviral therapy [10,35].

In summary, as NNRTI-based therapy is potent, incident resistance at moderate-to-high levels of adherence is uncommon – most of these individuals have complete viral suppression. Thus, in a population initiating NNRTI-based therapy, incident resistance is most common in individuals with low levels of adherence because these are the individuals failing therapy. NNRTI resistance mutations confer a high fold-change in resistance and have relatively little impact on viral fitness; thus, NNRTI-resistant viruses predominate in viremic individuals at all clinically relevant adherence levels. Finally, first-generation NNRTIs have a low-genetic barrier to resistance so, in the setting of viremia, a large proportion of individuals develop resistance.

Deoxycytidine analogue nucleoside reverse transcriptase inhibitors

In the CPCRA FIRST trial, the risk of NRTI resistance (82% was resistance to lamivudine [9]) was 4.5 times higher in individuals with 0–79% adherence and 2.5 times higher in individuals with 80–99% adherence compared with individuals with 100% adherence, a pattern similar to NNRTIs [34]. King *et al.* [32] assessed the relationship between adherence and the development of lamivudine resistance in a clinical trial setting. In their study, the peak incidence of lamivudine resistance occurred in individuals with 75–85% adherence. No individuals in this study had low adherence levels making the risk of resistance hard to assess in this population. However, an analysis of a retrospective cohort in British Columbia supported that lamivudine resistance is less likely to be detected at very low adherence levels [36].

In summary, the potency of lamivudine (and presumably emtricitabine) makes viremia and resistance at high levels of adherence unlikely. In viremic individuals with low-to-moderate levels of adherence, resistant virus predominates. This is true because the fold-change in resistance is very high in the setting of the major mutation conferring lamivudine resistance, the M184V. The fold-change in fitness is also very high, allowing a transition to wild-type HIV-1 at very low adherence levels. The low-genetic barrier to resistance makes resistance relatively common in those failing therapy. Finally, there appears to be a different rate of resistance development to deoxycytidine analogues depending on the other regimen components; this will be discussed further shortly.

Adherence–resistance relationships during multidrug therapy

Understanding class-specific adherence–resistance relationships lays the foundation for understanding these relationships during multidrug therapy. In addition to the factors mentioned previously, two other factors impact adherence–resistance relationships during multidrug therapy: the potential for differential drug exposure and the impact of the other regimen components.

Potential for differential drug exposure

Differential drug exposure refers to periods of single or dual-drug coverage during treatment with combination antiretroviral therapy. Antiretroviral therapy containing one or two drugs is associated with an increased risk of virological failure and the development of antiretroviral resistance [37–39]. Potential causes of differential drug exposure include differences in

pharmacokinetic characteristics of individual regimen components, differential adherence, and drug–drug interactions.

As adherence declines, dosing becomes more intermittent, allowing an increased chance for single and double-drug exposure to medicines with longer half-lives (Fig. 3). A similar circumstance occurs when an individual stops all antiretroviral medications. Two studies [40,41] have shown that interruptions in therapy are associated with the development of NNRTI resistance. In a third study [42], an interruption of 15 days conferred a 50% chance of viral rebound among suppressed patients on NNRTI-based therapy (Fig. 4), making these individuals predisposed to developing resistance. Clinically, asymmetrical half-lives may be the most important determinant of differential drug exposure at lower levels of adherence. It can increase the risk of NNRTI single-drug exposure on NNRTI-based therapy such as efavirenz + lamivudine + zidovudine (Fig. 3a) and the risk of deoxycytidine analogue single-drug exposure on protease inhibitor-based therapy such as lopinavir/ritonavir + lamivudine + zidovudine (Fig. 3b). A commonly used initial regimen consisting of efavirenz + tenofovir + emtricitabine has been very successful and this may be due in part to the symmetrically long half-lives (>36h) of all these medications. Importantly, the half-lives of intracellular NRTI triphosphates are the clinically relevant profile for NRTIs. The intracellular NRTI triphosphate half-lives are two to more than 10-fold longer than the NRTI half-lives in plasma [43].

Patients may choose to take some medications and not others – ‘differential adherence’. From 15 to 29% of individuals have different levels of adherence to individual components of a multidrug antiretroviral regimen [44,45]. Differential adherence is associated with an increased risk of virological failure and the development of antiretroviral resistance [45]. In a large prospective clinical trial, participants who self-reported differential adherence more than once prior to first virological failure were twice as likely to have antiretroviral resistance at first failure [45]. Factors associated with differential adherence include adverse drug events, three-times daily drug dosing, and lower baseline CD4 lymphocyte count [44]. It also appears more likely to occur with NNRTIs and protease inhibitors, rather than NRTIs [44]. Differential adherence appears to be relatively common and is clinically relevant.

The examples here are related to patterns of antiretroviral nonadherence. Differential drug exposure can also occur due to differences in absorption, distribution, metabolism, or elimination of individual regimen components. Drug–drug interactions and pharmacogenetic-antiretroviral associations can also predispose to differential drug exposure [46]. These relationships are important but not the focus of this review.

Additional regimen components

Data suggest that the characteristics of the other regimen components affect the propensity for the development of drug resistance mutations. For example, in a randomized controlled trial comparing lopinavir/ritonavir with nelfinavir, both in combination with lamivudine and stavudine, 82% of individuals failing nelfinavir between weeks 24 and 48 developed lamivudine resistance compared with 41% of individuals failing lopinavir/ritonavir [47]. These differences are likely based on both potency and the genetic barrier to antiretroviral resistance of the companion medications. Greater potency and higher genetic barrier to resistance prevent accumulation of drug resistance mutations to companion medications.

Final considerations

Several factors determine class-specific adherence–resistance relationships. First, antiretroviral regimen potency is important, as individuals with very low levels of viral replication are unlikely to develop resistance. Second, in the setting of viremia, circulating viral populations are determined by the interplay of the fold-change in resistance and fold-

change in fitness caused by drug resistance mutations. Third, the genetic barrier to antiretroviral resistance determines the rate of development of resistance mutations at levels of drug exposure that favor resistant over wild-type virus. During multidrug therapy, differential drug exposure increases the likelihood of developing resistance. Long half-life drugs, in the presence of short half-life drugs, may be particularly susceptible to the development of resistance at low-adherence levels due to periods of differential drug exposure during intermittent dosing. Finally, antiretroviral medications with higher potency and higher genetic barrier to resistance decrease the incidence of resistance for companion antiretroviral medications.

The complexities of adherence–resistance relationships are related to characteristics of the virus, the medications, and to their interactions. Despite this complexity, adherence–resistance relationships have been consistent using diverse methods of adherence assessment (electronic prescription bottle caps, pill-count, self-report, or pharmacy refill data), study methodology (cross-sectional or prospective), and type of resistance testing (genotypic or phenotypic).

It is also important to understand the type of study when evaluating adherence–resistance relationships. Incident resistance describes new resistance mutations accumulating over time in individuals initiating antiretroviral therapy. Prevalent or cross-sectional resistance describes resistance present in individuals at the time they fail antiretroviral therapy. Both perspectives are useful in settings with limited availability of resistance testing, such as in many resource-poor settings, and in resource-rich settings in which loss to follow-up, transfers of care, and cyclical engagement in healthcare are common [48].

The World Health Organization supports a public health approach for the treatment of HIV infection [49], which necessitates that salvage therapy for a population be chosen in a way that provides effective treatment for most of the individuals [50]. This requires knowledge not only of typical adherence levels and adherence patterns, but also an understanding of what types of resistance are predicted in individuals failing a particular therapy. Although some of this knowledge can be gained through experience, an understanding of the mechanisms behind adherence–resistance relationships may make it possible to predict expected resistance patterns for new medications and new classes of medications in the future. This understanding may also facilitate clinical trial design, including designs used to evaluate antiretroviral regimen sequencing and the use of specific combinations of medications, such as designing regimens with symmetrical half-lives. Following are brief examples of the application of this information for these purposes.

Predicting adherence–resistance relationships for other antiretroviral agents

Unknown adherence–resistance relationships can be hypothesized based on knowledge of drug potency, the fitness of resistant virus, and the genetic barrier to antiretroviral resistance (Table 1).

- (1) Nucleoside/nucleotide analogues other than the deoxycytidine analogues are mostly of moderate potency; there is impaired fitness with resistance and a moderate genetic barrier to resistance. This pattern is most similar to that of nonboosted protease inhibitors, so resistance would be expected at moderate-to-high levels of adherence.
- (2) Enfuvirtide is of high potency, resistant virus has impaired fitness, and the genetic barrier to resistance is low. This pattern is most similar to the deoxycytidine analogue NRTIs, so resistance would be expected to occur at moderate levels of adherence.
- (3) Raltegravir is of high potency, resistant virus has impaired fitness [51], and there is a low genetic barrier to resistance. This pattern is most similar to the deoxycytidine analogue NRTIs, so resistance would be expected to occur at moderate levels of adherence.

(4) Etravirine is of high potency, fitness of mutated virus is not impaired, and the genetic barrier to resistance is moderate. This pattern predicts a similar adherence–resistance relationship to other NNRTIs except that the increased barrier to resistance would make the incidence of resistance lower at all adherence levels.

(5) Maraviroc is of high potency but the fitness of mutated virus is hard to predict. The resistance pathways are complex and include overgrowth of low-frequency populations that use the CXCR4 coreceptor [52]. In addition, some mutations allow the mutant virus to preferentially use drug-bound CCR5 [53]. For these reasons, it is not possible to predict the adherence–resistance relationship for this class of drugs.

Clinical implications

In the absence of preexisting resistance, poor adherence is the major risk factor for virological failure and the development of resistance. Table 2 shows the expected risks for resistance with typical initial drug combinations. Overall, resistance is most common for NNRTIs and deoxycytidine analogue NRTIs, followed by nonboosted protease inhibitors and nondeoxycytidine analogue NRTIs, and is least common for boosted protease inhibitors. Table 2 also presents potential associations between differential drug exposure, due to asymmetric medication half-lives or differential adherence, and the development of class-specific resistance.

Integrase inhibitors are currently being studied as initial therapy for HIV-1 infection [54]. The adherence–resistance relationship for integrase inhibitors is expected to be similar to deoxycytidine NRTIs. Based on the relatively short serum half-life of raltegravir, the potential for differential drug exposure based on pharmacokinetics should be similar to protease inhibitors. However, the situation may be more complex as recent evidence suggests that raltegravir is essentially an irreversible inhibitor of HIV-1 DNA integration [55]. Differential adherence is unlikely, as raltegravir appears well tolerated. These characteristics suggest that resistance will be common in individuals failing integrase inhibitors and this has been seen in heavily pretreated patients [56]. Limited data suggest that dual-class resistance at first failure may also be relatively common [54].

Limitations

There are several important gaps in our current knowledge. Adherence–resistance relationships in the setting of transmitted or preexisting mutations may differ. Also, most studies have assessed class-specific relationships in the setting of antiretroviral regimens composed of a nucleoside backbone and one other component. How alternative combinations as initial or salvage therapy will interact is unclear. Recent studies have only begun to explore patterns of nonadherence, such as treatment gaps and differential adherence, which may be important in creating differential drug exposure leading to resistance. Adherence–resistance relationships for newer antiretroviral agents are not well characterized; future research should help to delineate these relationships. Finally, to date studies reporting adherence–resistance relationships have used traditional resistance assays with sensitivities down to 10–20% of the circulating viral population. Failure with ‘susceptible’ virus as defined by standard assays may hide a more complex mixture of circulating and/or archived resistant viruses that could impact the effectiveness of future treatment regimens [57]. More sensitive resistance assays are now available and will help to further delineate class-specific adherence–resistance relationships.

Conclusion

Existing research has laid the groundwork for a deeper understanding of the complex interplay between adherence and resistance. Information about newer medications and new classes of medications should prove useful in clinical practice and research settings. It may also suggest

lines of investigation for the treatment of other pathogens for which drug potency, pathogen resistance, host or pathogen genetics, or differential adherence are important. The goal of antiretroviral therapy remains complete virological suppression. However, knowledge of class-specific adherence–resistance relationships will help clinicians and patients tailor therapy to match individual patterns of adherence in order to minimize the development of resistance at failure. This information should guide the selection of optimal drug combinations and regimen sequences to improve the durability of antiretroviral therapy.

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Fig. 1.

The average ratio of luciferase activity of viruses obtained from individuals with phenotypically defined drug-resistant HIV (resistance) relative to luciferase activity of drug-susceptible virus (reference) is shown at various drug concentrations. The dotted line corresponds to a luciferase ratio of 1; luciferase ratios above this level imply that the resistant virus is more fit than the wild-type virus. The range of adherence levels (1–100%) corresponding to protein-adjusted C_{min} is shown in each figure; (a) nevirapine and (b) nelfinavir [23].

Fig. 2. Prevalence of complete viral suppression (HIV-RNA <50 copies/ml, light gray) and virological failure with (black) and without (dark gray) drug resistance by adherence quartile and drug regimen: (a) patients treated with nonnucleoside reverse transcriptase inhibitor (NNRTI); (b) patients treated with protease inhibitor [23]. gr2

Fig. 3.

Theoretical example of effect of different half-lives on drug exposure during a period of poor adherence ($\approx$, every 96h) with multidrug antiretroviral therapy. For simplification, peak drug concentrations and the zones of potential replication were standardized, despite differences by medication *in vivo*. Half-lives are as follows: dashed line=22h (approximate intracellular half-life of lamivudine triphosphate), dotted line=7h (approximate intracellular half-life for zidovudine triphosphate), solid line figure (a)=47.5h (approximate half-life of efavirenz), solid line figure (b)=5.5h (approximate half-life of lopinavir with ritonavir).

Fig. 4.

Predicted and observed probability of maintaining viral control (HIV RNA < 400 copies/ml) according to the longest interval of treatment discontinuation in individuals with viral suppression on nonnucleoside reverse transcriptase inhibitor (NNRTI)-based combination antiretroviral therapy. gr4 Based on this logistic model, a treatment interruption of 15 days was associated with a 50% probability [95% confidence interval (CI) 15%, 86%] of virological rebound [42].

Table 1
Proposed adherence–resistance relationships for drug classes and individual newer antiretroviral medications.^a

Drug potency ^b	Viral fitness ^c	Genetic Barrier ^d	Incident resistance: assessed prospectively	Prevalent resistance: assessed at failure	Medication examples
Moderate	Decreased	Low-to-moderate	Highest risk at moderate-to-high adherence	Highest risk at high levels of adherence	Nonboosted PIs, non-deoxycytidine NRTIs ^e
High	Decreased	Moderate-to-high	Resistance uncommon, highest risk at moderate-to-high adherence	Resistance uncommon, highest risk at high levels of adherence	Boosted PIs
High	Retained	Low	Highest risk at low levels of adherence	High risk at all levels of adherence	NNRTIs
High	Decreased	Low	Highest risk at moderate levels of adherence	Highest risk at low-to-moderate adherence	Deoxycytidine NRTIs, enfuvirtide ^e , raltegravir ^e
High	Retained	Moderate	Highest risk at low levels of adherence	Moderate risk at all levels of adherence	Etravirine ^e

NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside analogue reverse transcriptase inhibitor.

^a Maraviroc not included; predicted adherence–resistance relationship is complex.

^b Drug potency refers to the ability to suppress viral replication below limits of detection.

^c Viral fitness refers to the fitness of resistant virus compared with wild-type HIV-1.

^d Genetic barrier refers to the barrier to the development of high-level resistance.

^e Hypothesized relationship – little clinical data available.

Table 2

Likelihood of resistance at initial virological failure and likelihood of differential drug exposure and differential adherence based on regimen composition.

	Class of resistance at first failure	Likelihood of differential drug exposure^a	Likelihood of differential adherence^b
Nonboosted PI + NRTIs	Deoxycytidine NRTI > PI > other NRTI	Highest for longer half-life drugs such as deoxycytidine analogue NRTIs	PI > other NRTI > deoxycytidine NRTI
Boosted PI + NRTIs	Deoxycytidine NRTI > other NRTI >> PI	Highest for longer half-life drugs such as deoxycytidine analogue NRTIs	PI > other NRTI > deoxycytidine NRTI
NNRTI + NRTIs	NNRTI, deoxycytidine NRTI > other NRTI	Highest for longer half-life drugs NNRTIs followed by deoxycytidine analogue NRTIs	NNRTI > other NRTI > deoxycytidine NRTI (protected by fixed dose combinations)

^aDue to intermittent therapy with drugs having different half-lives.

^bDifferential adherence likelihood based on propensity for adverse drug events and daily dosing schedule of commonly used agents, which are protease inhibitor (PI), nucleoside analogue reverse transcriptase inhibitor (NRTI), and nonnucleoside reverse transcriptase inhibitor (NNRTI).