HIV Antiretroviral Drug Resistance

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Introduction

Highly active antiretroviral therapy (HAART) is the current standard of care for human immunodeficiency virus (HIV) infections. Although drug resistance may have been present before the introduction of antiretroviral (ARV) therapy due to random genetic variation, the introduction of ARV therapy exerts selective pressure over viral subpopulations to develop resistance. The use of HAART decreases the risk of resistance when compared with mono or dual therapy regimens. However, drug resistance remains an undesirable outcome of long-term therapy. Understanding and applying general principles in the proper use of ARV therapy will lessen drug resistance. While initially patients and clinicians have multiple regimens available to them, challenging situations arise when patients develop adverse reactions, intolerance, and decreased adherence and are choosing a new regimen to replace a failing one. The following review will describe some of those challenges from the perspective of HIV resistance.

Definition

Drug resistance in HIV is defined as a reduced susceptibility to a specific ARV [1] and has been documented since the introduction of ARV therapy [2]. Resistance mutations have been identified in all the major classes of ARVs [3]. The prevalence of drug resistance in treatment naïve HIV-1 infected patients in the United States has been reported to range between 4.3-15% [4-8]. The most common resistance associated mutations are within the non-nucleoside reverse transcriptase inhibitors (NNRTIs) drug class, followed by the nucleoside reverse transcriptase inhibitors (NRTIs) and the protease inhibitors (PIs) [6]. The prevalence of resistance to integrase inhibitors in naïve HIV positive patients is infrequent [9,10].

Types of resistance

Resistance may be intrinsic, such as the lack of activity of certain NNRTIs against HIV 2 virions [11,12]. The mechanism of resistance is due to a different structural fold in the HIV-2 reverse transcriptase hydrophobic pocket that does not allow some of the NNRTIs to bind [13]. Resistance can also be transmitted [14]. Resistance is influenced by natural genetic variability and can evolve with pharmacologic pressure from starting or stopping ARVs [15].

In order to prevent resistance, several drugs are combined to treat HIV infected patients. The rational for the use of at least three ARVs is that viral subspecies are less likely to accumulate mutations to all three drugs [16]. The use of three drugs that have different mechanisms of action is also more likely to arrest HIV replication [17,18]. Synergy (i.e. when 2 or more drugs can create an effect that none of them alone is able to attain) is another potential benefit that has been reported in vitro but the clinical significance of this remains to be seen [19].

Importance of resistance

Patients with multidrug resistant HIV have higher risk of death and poorer immunological and virological status as compared with other HIV infected patients [20]. The consequence of uncontrolled resistant viral replication is immunologic failure [21] with cases of multidrug resistant HIV-1 progressing rapidly to acquired immune deficiency syndrome (AIDS). The further potential is then for increasing transmission of resistant strains within a given population [22, 23].

The most common class of resistance is within the NNRTIs. Primary NNRTI resistance has been more frequently detected following single drug nevirapine perinatal prophylaxis [24,25]. NNRTIs such as nevirapine and efavirenz have a low barrier to resistance due to the requirement of only a single specific point mutation that may confer resistance to both [26].

The loss of available treatment regimens remains a concern with the widespread use of ARVs even though resistance levels vary. Resistance has been reported to be limited in low and middle-income countries to 3.7% when compared with the 10-20% rates in Europe and the United States [27]. More recently, an increasing trend has also been reported for transmitted ARV drug resistance in developing countries of 3-20% [28-30]. The differences between higher and lower income countries may be partially explained by the length of exposure to ARVs in different areas of the world. Transmission of drug resistant strains from mother to infant (perinatal transmission) has also been documented [27].

Independent predictors of ARV resistance [31] have been described and include: lower HIV-1 transmission in heterosexuals as compared to injection drug users, previous treatment experienced individuals, patients on suboptimal therapy, users of NNRTIs or patients with higher viral loads.

When resistance develops, the minority mutant populations within a heterogeneous HIV population become common [32,33]. This is due to the presence of continuous ARV therapy that prevents the wild virus from replicating while the mutant virus proliferates unabashedly [32,34,35].

The characteristics that facilitate the development of resistance include the existence of HIV subtypes, the rapid replication capacity (the ability of the virus to replicate itself efficiently, i.e. the fitness of the virion), a lower genetic barrier for developing resistance to some ARVs and an inefficient process of viral replication that can cause increased mutation selection under pharmacological pressure [35]. Whether HIV subtypes play a significant role in the development of resistance is still controversial.

Mutations can develop in a single step such as with some NNRTIs,

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but can also develop on a continuum with the accumulation of multiple mutations leading to virological failure as can be seen with the PIs [36]. Etravirine, a second generation NNRTI, requires the accumulation of more than one mutation prior to losing any susceptibility.

Clinically, resistance becomes evident when the viral load increases (virologic failure), the CD4 drops (immunologic failure) or when opportunistic infections or HIV related complications develop (clinical failure) [37].

**Causes of resistance**

The World Health Organization (WHO) has listed the following conditions as factors that increase the development of drug resistance [1]:

- Treatment with <3 drugs
- Inappropriate selection of drugs
- Adding one drug to a failing regimen
- Interruption of treatment
- Prolonging the use of a failing regimen

**Mechanisms of resistance**

The HIV virion has two properties that increase its ability to develop ARV resistance: error prone copying and high rates of viral replication. HIV is nonselective during copying and creates 1 error per each round of copying which may be base substitutions, insertions or deletions [35]. It also has a high rate of replication with up to several billion particles being produced per day [16]. The combination of high rate of viral replication and error prone copying leads to multiple variants of the virus known as quasi species. Each mutation has the potential to be significant in the development of drug resistance. Any mutation with a selective advantage will allow the virus to proliferate even in the presence of ARV therapy.

An excellent review by Clavel [16] of the specific mechanisms of drug resistance by class of ARVs can be found, although the basic mechanisms can be distilled down to include:

1. A modulatory effect at the drug binding site.
2. An enzymatic activity that can remove the drug from its binding site.
3. A size change in the drug binding site causing inability to compete for the enzyme.

**Viral cost of resistance**

The downside of developing resistance for the virus is that the mutations can decrease its replicative capacity. Fitness and resistance are the result of selective pressure on the virus caused by the presence of ARV therapy. Resistance mutations deprive the wild type virus (i.e. virus that does not have mutations and has 100% replicative capacity) of some of its survival advantage. Resistant viral quasi species with limited replicative capacity, however, may have survival advantage over more fit wild type virus when ARVs are given [34]. In the presence of resistance, if ARV therapy is stopped, the wild type virus rapidly reverts and replaces the mutant subspecies as the dominant form [34]. When the wild type virus returns, the previously developed resistance mutations are archived in the mutant virus quasi species. These mutations are likely to re-emerge if pharmacologic pressure then is re-introduced [34,38]. If a virus is resistant to all known ARVs, then there may be a role for the use of a failing ARV regimen with the goal of less efficient viral replication but this approach needs further investigation [38].

**Resistance tests**

There are several ways to test for resistance: genotype, phenotype, virtual phenotype and integrase inhibitor resistance sequencing tests. Genotype, phenotype and virtual phenotype testing are used for NRTI, NNRTI and PI resistance mutations. Genotype testing looks at the point mutations of the virus [39] whereas phenotype testing takes the virus and attempts to grow the virus in the presence of a single drug [39]. There are no prospective comparative effectiveness studies evaluating these alternatives, but the use of genotyping is currently preferred over phenotype testing for resistance based on availability, cost and sensitivity [40]. Phenotype testing may add further information to guide decision making. However, it may not add new information to the genotype result or it may only give confusing results by only detailing single drug resistance when in actuality a combination of drugs may yield hypersensitivity (i.e. lamivudine resistance can cause increased sensitivity to zidovudine) [41]. Still, it may add valuable information to generate a treatment plan in a heavily treatment experienced patient [42]. Virtual phenotypes are genotypes that are linked to known databases. These databases predict phenotypic resistance and are helpful in interpreting genotypes in the treatment experienced patient [40].

The accumulation of complex multiple resistance mutations make the use of databases essential for practitioners [43]. Neither genotype nor phenotype resistance testing overcome the barrier of detecting viral minority subspecies (i.e. if a virus subspecies is present in less than <20% of the virion population) [40]. Further, most tests require an HIV viral load of greater than 500-1,000 copies/ml. This highlights the importance of keeping complete ARV records as well as previously archived mutations to guide the choice of future ARV therapy.

Genotype testing is recommended in acute HIV infection, ARV naive patients with chronic HIV infection at the time of entry into HIV care, in patients with virologic failure or suboptimal suppression of viral load and in HIV infected pregnant women. Phenotype testing is currently recommended when complex drug resistance patterns are present or suspected in treatment experienced patients [40].

Currently available genotype, phenotype and virtual phenotype testing do not address integrase inhibitor or CCR5 co-receptor antagonist resistance. Testing for integrase inhibitor resistance is not included in the standard genotypic testing and has to be requested separately as an HIV-1 Integrase Inhibitor Resistance by Sequencing Test. The current Department of Health and Human Services (DHHS) guidelines do not recommend resistance testing for integrase inhibitors in treatment naive patients.

The Trophile ES assay (Monogram Biosciences) tests for CCR5 co-receptor tropism but requires a viral load of preferably greater than 1,000 copies/ml [44]. The newer Trophile DNA assay (Monogram Biosciences) however, may be used even if the viral load is undetectable, such as the case of a patient receiving an optimal drug regimen but needing to be switched because of an adverse drug effect. However, once started on a CCR5 co-receptor antagonist (after tropophile testing confirms CCR5 tropism), there are no resistance tests available for the CCR5 co-receptor antagonists should resistance develop [40]. It is important to recognize that testing for resistance is only available in resource rich settings.

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The transmissibility of resistance is of great concern. A viral population with multiply resistant mutations may create a significant public health problem [14]. The initial fear about transmissible resistance by the widespread availability of ARVs in developing countries has not fully emerged, but recent evidence from a multicenter cohort study in six African countries suggests an association between pretreatment viral resistance, virological failure and the development of drug resistance highlighting the need of increased access to genetic testing, ongoing surveillance and improved access to ARV therapy in developing countries [45]. Interestingly, resistance may be more frequent where many different ARVs are available to private practitioners as compared to countries where a universal public health approach is used [46]. None-the-less, the USA trend of increased prevalence of resistance in ARV naïve patient populations with higher access to health care (14%) and in partners who received ARV therapy (15%) is worrisome [4].

Knowledge of drug resistance patterns

Knowledge of drug resistance mutations is essential in selecting an appropriate ARV regimen for an HIV positive patient. However, the understanding of resistance is still incomplete. Bridging ARV regimens in patients with virological failure due to extensive resistance and intentionally selecting certain mutation patterns modulating viral fitness when virus suppression is not possible are interesting but poorly understood concepts [38]. Our knowledge of resistance is limited by the incomplete correlation between the presence of specific genotypic mutations and the prediction of resistance on clinical grounds [47,48]. Treatment algorithms, databases and expert opinions can all assist in the interpretation of complex mutation patterns [40]. The importance of individual and combinations of mutations with the complexity of interpretation needs further evaluation [49]. There are several databases that can be used to look for specific mutations and these are constantly updated including the Los Alamos national security operated database [50] and the Stanford University database [43].

The nomenclature for resistance mutations is standardized. The first letter describes the amino acid in the wild type virus. The following number describes the new amino acid substitution on the mutated virus. As an example, the mutation M41L describes a substitution of wild type amino acid Methionine at the position 41 to Leucine thereby conferring resistance [51]. Table 1 shows examples of key mutations for the main ARVs still in use today. A comprehensive and frequently updated resource for HIV-1 mutations is published elsewhere [51].

Conclusions

The treatment of HIV has become increasingly complex with the introduction of new ARVs and classes of drugs. An astute clinician needs to understand ARV drug resistance development in order to effectively combat HIV infections. By understanding not only the innate ability of HIV to develop resistance due to error prone copying and high replicative ability but also the factors that can increase drug resistance such as poor adherence and suboptimal regimens, the clinician will be better able to avert treatment failure. The use of drug histories, genotypes, phenotypes, virtual phenotypes, integrase inhibitor resistance by sequencing, Trophile ES and Trophile DNA assays along with Gene Sequencing Databases and expert consultation provide the tools needed to construct effective regimens. While the interpretation of mutations may be difficult and complex, it is essential to provide highly-treatment-experienced patients with their best options for successful therapy. Clinicians will need to keep abreast of advances in HAART and the subsequent ARV drug resistance as development of ARVs with longer drug half lives that permit less frequent dosing, fewer side effects, less expensive regimens and newer drug targets are found in order to use these resources wisely and effectively.

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**Table 1:** Common major HIV-1 resistance mutations of ARV drugs.

| ARV Class | Common Resistance Mutations |
|-----------|----------------------------|
| NRTI      | K65R, L74V, Y115F, M184V    |
|            | K65R, M184V                 |
|            | Lamivudine K65R, M184V       |
|            | Tenofovir K65R, K70L         |
|            | Zidovudine M41L, D67N, K70R, L210W, T215V/F, K219Q/E |
| NNRTI     | Efavirenz K103N              |
|            | Etravirine L100I, K101P, Y181C/I/V |
|            | Nevirapine K103N             |
|            | Rilpivirine K101E/P, E138A/G/K/Q/R, 179L, Y181C/I/V |
| PI         | Atazanavir +/- Ritonavir I50L, I84V, N88S |
|            | Darunavir/Ritonavir I47V, I50V, IS45/M/L, L76V, I84V |
|            | Lopinavir/Ritonavir V32I, I47V/A, L76V, V82A/F/T/S |
|            | Integrase Inhibitor           |
|            | Raltegravir Q148H/K/R, N155H |

(adapted from Johnson VA (51))
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