Journal of
AIDS & Clinical Research
ISSN: 2155-6113

Campo et al., J AIDS Clinic Res 2012, S5
DOI: 10.4172/2155-6113.S5-002

Review Article Open Access

HIV Antiretroviral Drug Resistance

Jose E Campo, Christine Jamjian and Claudia Goulston*
Division of Infectious Diseases, University of Utah, USA

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 naive 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 naive 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,

***Corresponding author:** Claudia Goulston M.D., Associate Professor, University of Utah, Division of Infectious Diseases, 30 N 1900 E SOM 4B319, SLC, UT 84132, USA, Tel: (801) 585-0448; Fax: (801) 585-3377; E-mail: Claudia.Goulston@hsc.utah.edu

Received November 18, 2011; **Accepted** January 16, 2012; **Published** January 20, 2012

Citation: Campo JE, Jamjian C, Goulston C (2012) HIV Antiretroviral Drug Resistance. J AIDS Clinic Res S5:002. doi:10.4172/2155-6113.S5-002

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 rebounds 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 trophism 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 trophile 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.

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 naive patientsin 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 represents the RNA position on the virion. The letter following the 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].

ARV Class	Common Resistance Mutations
NRTI	
Abacavir	K65R, L74V, Y115F, M184V
Emtricitabine	K65R, M184V
Lamuvidine	K65R, M184V
Tenofovir	K65R, K70L
Zidovudine	M41L, D67N, K70R, L210W, T215Y/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, I54M/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))

Table 1: Commonmajor HIV-1 resistance mutations ofARV drugs.

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.

References

1. Organization WHO (2012) HIVDR Module 1 Introduction to HIVDR.
2. DeGruttola V, Dix L, D'Aquila R, Holder D, Phillips A, et al. (2000) The relation between baseline HIV drug resistance and response to antiretroviral therapy: re-analysis of retrospective and prospective studies using a standardized data analysis plan. Antivir Ther 5: 41-48.
3. Vella S, Palmisano L (2005) The global status of resistance to antiretroviral drugs. Clin Infect Dis 41 Suppl 4: S239-246.
4. Weinstock HS, Zaidi I, Heneine W, Bennett D, Garcia-Lerma JG, et al. (2004) The epidemiology of antiretroviral drug resistance among drug-naive HIV-1-infected persons in 10 US cities. J Infect Dis 189: 2174-2180.
5. Huang HY, Daar ES, Sax PE, Young B, Cook P, et al. (2008) The prevalence of transmitted antiretroviral drug resistance in treatment-naive patients and factors influencing first-line treatment regimen selection. HIV Med 9: 285-293.
6. Wheeler WH, Ziebell RA, Zabina H, Pieniazek D, Prejean J, et al. (2010) Prevalence of transmitted drug resistance associated mutations and HIV-1 subtypes in new HIV-1 diagnoses, U.S.-2006. AIDS 24: 1203-1212.
7. Ross L, Lim ML, Liao Q, Wine B, Rodriguez AE, et al. (2007) Prevalence of antiretroviral drug resistance and resistance-associated mutations in antiretroviral therapy-naive HIV-infected individuals from 40 United States cities. HIV Clin Trials 8: 1-8.
8. Liu J, Miller MD, Danovich RM, Vandergrift N, Cai F, et al. (2011) Analysis of low-frequency mutations associated with drug resistance to raltegravir before antiretroviral treatment. Antimicrob Agents Chemother 55: 1114-1119.
9. Lataillade M, Chiarella J, Kozal MJ (2007) Natural polymorphism of the HIV-1 integrase gene and mutations associated with integrase inhibitor resistance. Antivir Ther 12: 563-570.
10. Cossarini F, Boeri E, Canducci F, Salpietro S, Bigoloni A, et al. (2011) Integrase and fusion inhibitors transmitted drug resistance in naive patients with recent diagnosis of HIV-1 infection. J Acquir Immune Defic Syndr 56: e51-54.
11. Ntemgwa ML, d'Aquin Toni T, Brenner BG, Camacho RJ, Wainberg MA

(2009) Antiretroviral drug resistance in human immunodeficiency virus type 2. Antimicrobial agents and chemotherapy. 53: 3611-3619.

12. Trevino A, de Mendoza C, Caballero E, Rodríguez C, Parra P, et al. (2011) Drug resistance mutations in patients infected with HIV-2 living in Spain. J Antimicrob Chemother 66: 1484-1488.

13. Ren J, Bird LE, Chamberlain PP, Stewart-Jones GB, Stuart DI, et al. (2002) Structure of HIV-2 reverse transcriptase at 2.35-A resolution and the mechanism of resistance to non-nucleoside inhibitors. Proc Natl Acad Sci U S A 99: 14410-14415.

14. Yerly S, Kaiser L, Race E, Bru JP, Clavel F, et al. (1999) Transmission of antiretroviral-drug-resistant HIV-1 variants. Lancet 354: 729-733.

15. Wainberg MA, Zaharatos GJ, Brenner BG (2011) Development of Antiretroviral Drug Resistance. N Engl J Med 365: 637-646.

16. Clavel F, Hance AJ (2004) HIV Drug Resistance. N Engl J Med 350: 1023-1035.

17. Carpenter CC, Fischl MA, Hammer SM, Hirsch MS, Jacobsen DM, et al. (1996) Antiretroviral therapy for HIV infection in 1996. Recommendations of an international panel. International AIDS Society-USA. JAMA 276: 146-154.

18. Staszewski S, Morales-Ramirez J, Tashima KT, Rachlis A, Skiest D, et al. (1999) Efavirenz plus Zidovudine and Lamivudine, Efavirenz plus Indinavir, and Indinavir plus Zidovudine and Lamivudine in the Treatment of HIV-1 Infection in Adults. N Engl J Med 341: 1865-1873.

19. Schader SM, Colby-Germinario SP, Schachter JR, Xu H, Wainberg MA (2011) Synergy against drug-resistant HIV-1 with the microbicide antiretrovirals, dapivirine and tenofovir, in combination. AIDS 25: 1585-1594.

20. Grover D, Copas A, Green H, Edwards SG, Dunn DT, et al. (2008) What is the risk of mortality following diagnosis of multidrug-resistant HIV-1? J Antimicrob Chemother 61: 705-713.

21. Pantaleo G, Graziosi C, Fauci AS (1993) The Immunopathogenesis of Human Immunodeficiency Virus Infection. N Engl J Med 328: 327-335.

22. Markowitz M, Mohri H, Mehandru S, Shet A, Berry L, et al. (2005) Infection with multidrug resistant, dual-tropic HIV-1 and rapid progression to AIDS: a case report. Lancet 365: 1031-1038.

23. Blick G, Kagan RM, Coakley E, Petropoulos C, Maroldo L, et al. (2007) The probable source of both the primary multidrug-resistant (MDR) HIV-1 strain found in a patient with rapid progression to AIDS and a second recombinant MDR strain found in a chronically HIV-1-infected patient. J Infect Dis 195: 1250-1259.

24. Eshleman SH, Mracna M, Guay LA, Deseyve M, Cunningham S, et al. (2001) Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET 012). AIDS 15: 1951-1957.

25. Micek MA, Blanco AJ, Beck IA, Dross S, Matunha L, et al. (2010) Nevirapine resistance by timing of HIV type 1 infection in infants treated with single-dose nevirapine. Clin Infect Dis 50: 1405-1414.

26. Deeks SG (2001) International perspectives on antiretroviral resistance. Nonnucleoside reverse transcriptase inhibitor resistance. J Acquir Immune Defic Syndr 26 Suppl 1: S25-33.

27. WHO (2012) HIV Drug resistance fact sheet.

28. Price MA, Wallis CL, Lakhi S, Karita E, Kamali A, et al. (2011) Transmitted HIV type 1 drug resistance among individuals with recent HIV infection in East and Southern Africa. AIDS Res Hum Retroviruses 27: 5-12.

29. Ndembi N, Hamers RL, Sigaloff KC, Lyagoba F, Magambo B, et al. (2011) Transmitted antiretroviral drug resistance among newly HIV-1 diagnosed young individuals in Kampala. AIDS 25: 905-910.

30. Hamers RL, Wallis CL, Kityo C, Siwale M, Mandaliya K, et al. (2011) HIV-1 drug resistance in antiretroviral-naive individuals in sub-Saharan Africa after rollout of antiretroviral therapy: a multicentre observational study. Lancet Infect Dis 11: 750-759.

31. Di Giambenedetto S, Zazzi M, Corsi P, Gonnelli A, Di Pietro M, et al. (2009) Evolution and predictors of HIV type-1 drug resistance in patients failing combination antiretroviral therapy in Italy. Antivir Ther 14: 359-369.

32. Meyerhans A, Cheynier R, Albert J, Seth M, Kwok S, et al. (1989) Temporal fluctuations in HIV quasispecies in vivo are not reflected by sequential HIV isolations. Cell 58: 901-910.

33. Brenner BG (2007) Resistance and viral subtypes: how important are the differences and why do they occur? Curr Opin HIV AIDS 2: 94-102.

34. Kijak GH, Simon V, Balfe P, Vanderhoeven J, Pampuro SE, et al. (2002) Origin of human immunodeficiency virus type 1 quasispecies emerging after antiretroviral treatment interruption in patients with therapeutic failure. J Virol 76: 7000-7009.

35. Preston BD, Poiesz BJ, Loeb LA (1988) Fidelity of HIV-1 reverse transcriptase. Science 242: 1168-1171.

36. Condra JH, Schleif WA, Blahy OM, Gabryelski LJ, Graham DJ, et al. (1995) In vivo emergence of HIV-1 variants resistant to multiple protease inhibitors. Nature 374: 569-571.

37. Haidara A, Chamberland A, Sylla M, Aboubacrine SA, Cissé M, et al. (2010) High level of primary drug resistance in Mali. HIV Med 11: 404-411.

38. Ross L, Elion R, Lanier R, Dejesus E, Cohen C, et al. (2009) Modulation of K65R selection by zidovudine inclusion: analysis of HIV resistance selection in subjects with virologic failure receiving once-daily abacavir/lamivudine/zidovudine and tenofovir DF (study COL40263). AIDS Res Hum Retroviruses 25: 665-672.

39. Richman DD (2004) Benefits and limitations of testing for resistance to HIV drugs. J Antimicrob Chemother 53: 555-557.

40. Adolescents PoAGfAa (2011) Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services 2011: 1-166.

41. Diallo K, Oliveira M, Moisi D, Brenner B, Wainberg MA, et al. (2002) Pressure of zidovudine accelerates the reversion of lamivudine resistance-conferring M184V mutation in the reverse transcriptase of human immunodeficiency virus type 1. Antimicrobial Agents and Chemotherapy 46: 2254-2256.

42. Coffin JM (1995) HIV population dynamics in vivo: implications for genetic variation, pathogenesis, and therapy. Science 267: 483-489.

43. HIV Drug Resistance Database (2012).

44. Whitcomb JM, Huang W, Fransen S, Limoli K, Toma J, et al. (2007) Development and characterization of a novel single-cycle recombinant-virus assay to determine human immunodeficiency virus type 1 coreceptor tropism. Antimicrob Agents Chemother 51: 566-575.

45. Hamers RL, Schuurman R, Sigaloff KC, Wallis CL, Kityo C, et al. (2011) Effect of pretreatment HIV-1 drug resistance on immunological, virological, and drug-resistance outcomes of first-line antiretroviral treatment in sub-Saharan Africa: a multicentre cohort study. Lancet Infect Dis [Epub ahead of print].

46. Bautista-Arredondo S, Mane A, Bertozzi SM (2006) Economic impact of antiretroviral therapy prescription decisions in the context of rapid scaling-up of access to treatment: lessons from Mexico. AIDS 20: 101-109.

47. Hirsch MS, Brun-Vezinet F, Clotet B, Conway B, Kuritzkes DR, et al. (2003) Antiretroviral drug resistance testing in adults infected with human immunodeficiency virus type 1: 2003 recommendations of an International AIDS Society-USA Panel. Clin Infect Dis 37: 113-128.

48. Haubrich R, Demeter L (2001) International perspectives on antiretroviral resistance. Clinical utility of resistance testing: retrospective and prospective data supporting use and current recommendations. J Acquir Immune Defic Syndr 26 Suppl 1: S51-59.

49. Zolopa AR (2003) Genotype-phenotype discordance: the evolution in our understanding HIV-1 drug resistance. AIDS 17: 1077-1078.

50. Los Alamos HIV Resistance database (2012).

51. Johnson VA, Calvez V, Gunthard HF, Paredes R, Pillay D, et al. (2011) 2011 update of the drug resistance mutations in HIV-1. Top Antivir Med 19: 156-164.

This article was originally published in a special issue, **Drug Resistance: HIV** handled by Editor(s). Dr. Claudia Goulston, University of Utah, USA