

CLINICAL REVIEW

Problems Associated with Human Immunodeficiency Virus Resistance to Antiviral Drugs

Mark A. Wainberg*, B.Sc., Ph.D.

INTRODUCTION

The fact that HIV (human immunodeficiency virus) can become resistant to antiviral drugs has given rise to a number of important concerns distinct from the obvious question of the relationship between drug resistance and treatment failure. A major issue is the extent to which drug-resistant viruses may be transmitted in primary infection via sexual or intravenous routes and how this relates to the relative fitness of such strains. It is also important to understand the potential role of effective antiviral therapy in the decrease of viral burden in both blood and sexual secretions, and the extent to which this may be compromised in individuals harboring resistant viruses. A related subject is the important role of patient adherence to antiviral therapy in achieving sustained reduction in viral load and preventing the emergence of drug resistance. The problem of limited drug access in developing countries adds an additional layer of complexity to this problem.

Diminished susceptibility of HIV-1 to antiviral drugs is directly attributable to amino acid changes in the viral reverse transcriptase (RT) and protease (PR) enzymes targeted by these compounds (1-4) (Table 1). The amino acid changes are in turn due to viral RT and PR gene mutations resulting from the high error rate of the viral RT that is responsible for copying the viral RNA genome (5,6). The mutation rate of HIV RT is between 10^{-4} and 5×10^{-5} , which means that 0.2 to 1 mutations can occur during each virion's replication event, given a viral genomic length of 2.9 kb (7).

Mutations are readily detectable under conditions of selective pressure, as exerted naturally by the immune

system or artificially by antiviral drugs. In the case of immunological pressure, HIV variants may emerge that are less recognized by immune effector mechanisms such as cytotoxic T lymphocytes and/or neutralizing antibodies. In the case of antiviral drugs, resistant HIV variants may emerge and be maintained under conditions of sustained replication and drug pressure. Mutations that result in drug-resistant variants can occur both prior to the administration of antiviral drugs as well as during therapy, so long as the antiviral regimens employed do not completely suppress viral replication. In the absence of selection pressure, such mutations exist only as a tiny proportion of a much larger quasi-species and may never be detected.

An important consideration in drug resistance relates to the concept of 'genetic barrier'. Among the reasons that high level resistance to certain drugs, such as zidovudine (AZT) and indinavir, takes relatively long periods (0.5 to two years) to develop is that multiple mutations must be present and selected for under conditions of therapy (8-10). This is in contrast with the development of very rapid resistance against other compounds such as 3TC, an RT nucleoside inhibitor, and nevirapine, a non-nucleoside RT inhibitor (NNRTI), where a single mutation is sufficient to confer very high level (e.g., 500-1000 fold) resistance (11,12). With both 3TC and nevirapine, when used as single agents, high level resistance can occur within one month of treatment initiation.

HIV-1 RESISTANCE IN PRIMARY INFECTION

Uncertainty exists as to the extent to which drug-resistant strains of HIV-1 are responsible for primary infection. This is true for relatively old agents, such as AZT, and even truer for newer ones such as 3TC and protease inhibitors. Nevertheless, the available findings

* To whom correspondence should be addressed: McGill University AIDS Centre, Jewish General Hospital, Montreal, Quebec, Canada H3T 1E2

Table 1. Drugs commonly used against HIV

Type of drug	Compound (manufacturer)	Year approved		Some mutations associated with resistance
		In USA	In Canada	
RT inhibitors				
Nucleosides	AZT (Glaxo-Wellcome)	1987	1989	M41L, D67N, K70R, T215Y, K219Q
	ddl (Bristol-Myers Squibb)	1991	1991	L74V
	ddC (Roche)	1992	1992	K65R, T69D
	d4T (Bristol-Myers Squibb)	1994	1995	V75T
	3TC (Glaxo-Wellcome)	1995	1995	M184V
Non-nucleosides	Nevirapine (Boehringer-Ingelheim)	1996	1998	L1001, K103N, V106A, V108I, Y181C, Y188C
	Delavirdine (Pharmacia-Upjohn)	1997	1998	K103N, K103T, Y181C, P236L
Protease inhibitors				
	Saquinavir (Roche)	1995	1995	G48V, 154V, 184V, L90M,
	Ritonavir (Abbott)	1996	1996	M361, M461, 154V, A71V, V82F, 184V, L90M
	Indinavir (Merck)	1996	1996	K20M, M46L, 154V, L63P, A71T, V82A, 184V, L90M
	Nelfinavir (Agouron)	1997	1998	D30N, M461, L63P, A71V, 184V, N88D, L90M

suggest that drug-resistant variants in primary infection are relatively uncommon. For example, studies in a number of Western European countries found that only 5-13% of HIV strains responsible for primary infection contain the T215Y mutation in RT associated with resistance to AZT (13). While this is a reflection of the wide-spread use of AZT in the treatment of HIV infection since the 1980s, it is noteworthy that the T215Y mutation associated with primary infection has not dramatically increased in frequency between 1989 and 1995. In fact, during 1995, none of the viruses evaluated from 26 cases of primary infection possessed this mutation (13). Possibly, current detection methods for HIV resistance in baseline populations are not adequately sensitive. But it is equally possible that drug-resistant viruses may be somewhat disadvantaged in regard to growth potential in newly infected individuals. Alternatively, wild-type viruses, in contrast to drug-resistant variants, may be preferentially transmitted. More studies are clearly needed in this important area.

The identification of drug-resistant HIV strains in previously untreated patients may have practical significance, especially if drugs used in treatment are ineffective against resistant strains acquired in primary infection. Initiation of treatment may then potentiate the rapid selection of pre-existing, low-level resistance. Post-exposure prophylaxis¹, related to either sexual contact or occupational needlestick puncture, may also depend on the resistance profile of the donor; virtually all individuals who receive AZT over prolonged periods may develop resistance against this drug (14,15). AZT is expected to be largely ineffective in individuals infected by AZT-resistant strains. This has been documented in cases of vertical transmission, from mothers to infants, as well as in cases of primary infection. It is now important to determine whether these findings also apply to HIV strains resistant to other drugs and to evaluate

whether viruses resistant to protease inhibitors can also cause disease. To date, only one case of primary infection associated with resistance to 3TC, attributable to the M184V mutation in RT, has been reported out of a total of approximately 30 cases studied (16).

Preventing vertical transmission of HIV from pregnant women to their offspring in another important issue². AIDS Clinical Trials Group (ACTG) (NIH) protocol 076 demonstrated conclusively that AZT can significantly diminish the transmission of HIV from pregnant women to their offspring, provided the drug is administered on a continuous basis throughout the third trimester followed by daily treatment of infants for two months after delivery (17).

An important question is the extent to which treatment of this type can now be initiated in resource-poor countries to prevent vertical transmission of HIV, given the difficulties of administering drugs over prolonged periods to both mothers and infants in such settings. One possibility is to evaluate short-term therapy, in which maternal AZT treatment is discontinued immediately following delivery. The alternative, i.e., continuing maternal AZT treatment post-delivery, would provide little additional clinical benefit due to almost certain emergence of high level AZT resistance. Thus, the limited and stringent use of AZT in this context might preserve the benefit of the drug in prevention of vertical transmission during future pregnancies. Local decision-making is an important consideration in these situations. In Western societies,

¹ *Editors' note:* Please see "Post-exposure Anti-Retroviral Chemoprophylaxis for the Human Immunodeficiency Virus: Rights, Duties, and Liabilities," by J. Herland in this issue [MJM 5: 46-51; 1999], online at www.mjm.mcgill.ca.

² *Editors' note:* Please see "The Use of AZT to Reduce the Risk of Vertical Transmission of Human Immunodeficiency Virus" by V. B. Rao [MJM 4: 38-45; 1998], online at www.mjm.mcgill.ca.

the current standard of care for HIV-infected pregnant women is triple drug therapy, including the use of a protease inhibitor. Such protocols are reported to virtually eliminate the likelihood of birth of HIV-infected infants (17).

CAN DRUG-RESISTANT VARIANTS OF HIV BE TRANSMITTED?

There is no direct evidence to date to suggest that drug-resistant strains of HIV are more transmissible than wild-type viruses and, in fact, the opposite conclusion can be inferred from the work cited above on transmission of AZT-resistant strains in primary infection between 1989 and 1995 (13). Otherwise, one would have expected to see a steady climb in the percentage of cases of primary transmission associated with mutations that confer resistance to ZDV during this period. Further, some data suggest that AZT-resistant strains may, in fact, be marginally impaired in regard to replication competence (18). In addition, viruses containing the M184V mutation, associated with resistance to 3TC, have been shown to be less replication-fit than wild type viruses in primary cells, e.g., peripheral blood mononuclear cells, although both types of viruses may multiply equally well in a variety of T cell lines (19,20). One case of sexual transmission of HIV resistant to both AZT and nevirapine has been reported (21).

Some have argued that the relatively restricted nature of the HIV quasi-species, seen soon after primary infection, may mean that primary infection with HIV is a relatively clonal event. This implies that only one predominant variant of HIV may be transmitted in primary infection. At the same time, it is well documented that the viruses that predominate in the blood in early stage infection are mostly of the non-syncytium-inducing (NSI) phenotype, while those that predominate during end-stage disease may possess a syncytium-inducing (SI) phenotype. This raises important questions about the mechanism of selection of NSI viruses in early stage disease. On the one hand, it might be argued that restriction in regard to such selection could be exerted at the level of the vaginal or rectal mucosa. However, restriction might also apply in regard to dendritic cells or the ability of viruses to infect and replicate in cells of monocytic and lymphocyte origin. On the other hand, intravenous drug users who are infected by HIV also have a preponderance of NSI viruses in their blood during primary infection. This suggests that the selection of NSIs is not related to vaginal or rectal mucosa or dendritic cells. One possibility is that SI viruses are cytopathic and cannot easily establish a reservoir in newly-infected hosts. It is also possible that SI viruses

may be better targets of immune destruction than NSIs during early stages of viral infection. Conceivably, as well, natural killer cells might play an important role in early stage infection by selectively targeting SI-infected cultures.

In addition to the foregoing, viruses that successfully establish primary infection, e.g., NSI variants, may have greater fitness than those that do not. These subjects, among others, need to be urgently explored.

EFFECTS OF ANTIVIRAL DRUGS ON VIRAL BURDEN IN VARIOUS BODY COMPARTMENTS

Effective treatment of HIV infected individuals with antiviral drugs can lead to decreases in the amount of virus detectable in blood, as measured by various tests available for quantitation of viral RNA copy number in body fluids (22,23). In contrast, the use of monotherapy or inadequate drug regimens can frequently involve a relatively small drop in viral burden, followed by a rise in the amount of detectable virus in blood concomitant with the development of drug resistance (24-26).

Combinations of three or more antiviral drugs in previously treatment-naïve patients have resulted in profound drops in viral burden that are sustained for prolonged periods, e.g., six months to two years or longer. In fact, several such studies have demonstrated that triple drug combination therapy can lower the amount of virus in blood to below limits of detection, using the most sensitive techniques available for this purpose, e.g., less than 20 copies of viral RNA per ml. In other studies, the use of antibacterial drugs to combat gonorrhea or other forms of urethritis have demonstrated significant diminutions in the amount of viral burden in genital fluids, but not blood, suggesting that concomitant bacterial infection may sometimes be a cofactor in high viral burden in genital secretions and sexual transmission of HIV (27).

Two excellent examples of triple combination antiviral drug effects have included the use of indinavir together with AZT and 3TC (28,29) or, alternatively, nevirapine together with AZT and ddI to treat previously drug-naïve individuals. In studies that involved well over 100 subjects, viral burden was shown to drop to below limits of detection in over 80% for the combinations which included indinavir and over 50% for that which included nevirapine. In the case of indinavir plus AZT plus 3TC, virus isolated from patients who properly adhered to their antiviral drug regimens were shown to be wild-type even two years after initiation of treatment in regard to each of phenotype and genotype for all of the drugs used (30,31). This is especially significant for 3TC, since viruses isolated from patients exposed to 3TC in less robust treatment regimens generally contain mutated

forms of RT, i.e., M184I or M184V, associated with resistance to 3TC (32). These changes commonly occur within one month of initiation of less durable treatment combinations. In the case of nevirapine, viruses from adherent individuals on triple regimens likewise contained wild-type phenotypes and genotypes for as long as six months after initiation of treatment (33,34). In both instances, these data show that the antiviral regimens had successfully blocked viral replication such that mutations that would normally encode drug resistance could not take place. These findings suggest that the viruses that had been isolated from the subjects in questions had remained dormant in latent viral reservoirs, raising the important issue of whether eradication of HIV might ever be possible in the context of the anti-viral drug regimens that are currently available.

It is of major public health concern to determine whether combination therapy might lead to reduction of viral burden in genital fluids, which are the most important vehicles for HIV transmission. While such a result might be predicted on the basis of the plasma viral burden data cited above, it is important to show this in a definitive way in studies performed on both vaginal fluids and ejaculate. Several studies have now provided such evidence. One report showed that high levels of viral RNA are usually present in the semen of HIV-infected men at all stages of disease, and that viral burden in semen increased concomitant with disease progression. The use of combinations of indinavir together with an NNRTI, Sustiva, resulted in profound reductions in viral burden in both semen and blood (35). A second report yielded similar results in a group of 44 individuals treated with a variety of antiviral drug regimens (36). This study also showed that patients who had non-detectable levels of viral RNA in blood also had non-detectable levels in semen.

PATIENT COMPLIANCE

Unfortunately, such encouraging results have not been obtained with patients who did not adhere to their antiviral regimens or who received less effective combinations of antiviral drugs, e.g., nevirapine plus AZT. In particular, non-adherence in regard to ddI in the triple combination of AZT plus ddI plus nevirapine resulted in both higher blood levels of viral RNA as well as the development of resistance against both nevirapine and AZT (33,34). This shows that the use of non-robust anti-retroviral therapy may commonly lead to the development of drug resistance. In addition, resistance has frequently been demonstrated in patients on triple combination therapies who had previously been treated with a variety of anti-viral compounds that had pre-selected a variety of resistance-conferring mutations (29,32,33)

DRUG ACCESS AND PEDIATRIC HIV DISEASE

The United Nations (UN) program on acquired immune deficiency syndrome (AIDS) stunned many observers recently when it announced that HIV-infected mothers in developing countries should consider alternatives to breast-feeding. Consensus opinion had held that no alternative to breast-feeding was possible, given that formula or cow's milk substitutes were either unavailable or unaffordable in most developing countries where HIV is endemic. Apparently, UN officials now consider that the risk to infants of HIV transmission through mother's milk outweighs the dangers associated with other methods of feeding infants. These dangers include the likelihood that powdered formula might be reconstituted with contaminated water. Cases of contamination caused the deaths of thousands of infants only a generation ago.

In fact, the problem is even worse than portrayed in the recent UN announcement, and UN recognition of the reality of HIV transmission through breast milk represents only one aspect of a complex situation.

Ironically, in recent years many scientists had boasted of the powerful effects of anti-HIV drugs in preventing the transmission of HIV from infected women to their infants during birth. Several studies have documented that the use of AZT to treat HIV-positive women during the latter months of pregnancy reduced the chances of such transmission by 51% to 68% (17). However, this benefit may be short-lived if babies born free of HIV acquire the virus afterward through breast-feeding (17).

The reality gets worse too. Scientists understand that almost all of the women in developing countries who receive AZT during pregnancy will not themselves benefit from this treatment. This is because no single drug can adequately counter the ability of the virus to replicate and mutate. These mutations can enable HIV to become resistant to the very drugs used to treat it. This is why almost all patients in North America receive a combination of three or more drugs, which has proven far more effective at keeping the virus at bay than single-drug treatment. The end result of treating women in Africa with AZT only can be the development of resistance to AZT and, ultimately, the transmission of the drug-resistant virus to previously uninfected individuals. This fact has important implications for public health.

However, in the absence of effective treatment, a high proportion of the women who harbor HIV will develop AIDS and die. What then will become of their children, whether HIV-infected or not? It is no secret orphans in the developing world confront problems far more severe than those that prevail in Western countries.

The World Health Organization estimates that approximately 18,000 people become infected by HIV

each day throughout the world and that about 1,600 HIV-infected infants are born each day. Almost none of these births takes place in the United States or in other countries in which access to antiretroviral drugs is not problematic. In fact, current treatment guidelines stipulate that HIV-infected pregnant women should receive the same types of triple drug combinations that are prescribed to other HIV-infected persons. The result has been a dramatic reduction of mother-to-offspring transmission of HIV in all Western countries. Most major medical centers in North America have reported that the percentage of infants born last year with HIV was less than 0.1 percent of total births. (Dr. James O. Kahn, University of California at San Francisco, personal communication).

In contrast, the epidemic of pediatric HIV disease in sub-Saharan Africa and other HIV epidemic areas continues to grow. Lack of effective treatment access in developing countries, coupled with ability of HIV to be transmitted at birth and through breast milk, ensures that the gaps between rich and poor countries in regard to the problem of HIV disease will grow wider.

For these and other reasons, the most important measures that should be taken in sub-Saharan Africa and other epidemic areas continue to be sex-education programs that inform the populations of the risks of HIV exposure. However, the types of safe-sex and HIV-awareness campaigns that exist in the United States are practically absent in most African countries, even though the HIV-infection rate in girls ages 13 to 17 in countries such as Zimbabwe is approximately 25 percent. To wait until these girls turn 18 before teaching them about sex is to ensure that more babies with HIV will be born.

Why do the downtowns of African cities such as Johannesburg and Harare lack billboards that promote the message of condom usage and safe sex of the type commonly seen in San Francisco and Chicago? Simply put, the governments of too many developing countries hit hard by HIV/AIDS lack the political will to get this message out. In some cases, politicians may object to safe-sex campaigns on religious or moral grounds, with the consequences that little or no action is taken, and the toll of HIV disease continues to increase.

In contrast, both Uganda and Thailand have embarked on free condom distribution and HIV-education campaigns, despite political opposition, and they report diminished rates of new HIV infections. The governments of Western democracies can help by putting pressure on countries in which the HIV epidemic is growing the fastest to quickly establish such programs. Failure to act will ensure that the numbers of children and infected by HIV will grow well into the 21st century.

CONCLUDING REMARKS

Studies performed to date suggest that combination

antiviral therapy might render adherent patients less infectious to their sexual contacts. This is important information, since a decreased HIV transmission rate is a goal in the management of HIV patients. Nevertheless, protected sex remains the recommended norm for HIV-infected individuals. It is hoped that accumulating data in support of the clinical benefits of full adherence to antiviral regimens, i.e., less viral burden as well as less likelihood of resistance, will further encourage and reinforce adherence. We must also hope that we will better manage the toxic side-effects of the drugs currently in use and that improved dosing schedules will be developed, such that quality of life considerations in regard to adherence will no longer be as problematic as has been the case in the past. Finally, we must endeavor to reduce differences between rich and poor countries in regard to both drug access and HIV education, as well as in other areas.

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Mark A. Wainberg, B.Sc., Ph.D., has made important contributions to the study of virus host interactions and anti-viral drug development. His research has helped to define conditions that govern differential infection by HIV of lymphocytic versus monocytic cell populations. He has also characterized HIV infected CD4 and CD8 sub-populations of T helper lymphocytes and dealt with the nature of anti-viral immune responsiveness in individuals infected by HIV. Dr. Wainberg's laboratory was among the first to characterize the phenomenon of HIV escape, through mutagenesis, from immunological pressure. Dr. Wainberg is recognized internationally for his research in the area of HIV drug development and drug resistance. He has been elected the president of the International AIDS Society for the period 1998-2000. He identified 3TC as an anti-viral drug in 1989, and has contributed to the international literature on drug action and drug resistance in AIDS, ranking 12th in the world for publications and being the only Canadian in the top 50 contributors. 3TC may be recognized as Canada's most important drug contribution since the discovery of insulin. His laboratory continues to work in the area of new drug discovery, vaccine development and prevention of HIV infection.