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Drug-resistant human immunodefiency virus

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Abstract

The development of antiretroviral therapy has led to a major reduction in human immunodeficiency virus (HIV)-related mortality. There are now six antiretroviral drug classes, with more than 20 unique antiretroviral drugs. However, HIV drug resistance occurs with all antiretroviral agents. Drug resistance can affect the response to antiretroviral therapy and is associated with increased mortality. The emergence of resistance in persons on antiretroviral therapy and the transmission of drug-resistant HIV strains to newly infected persons are now major public health concerns. Resistant variants that make up as little as 1% of the viral population in an HIV-infected person are clinically important, as they can rapidly grow under drug selection pressure and lead to therapy failure. However, current resistance assays used in the clinic reliably detect resistant variants only if they make up at least 20% of the circulating viral population. Recently, antiretroviral drugs have been developed that can inhibit HIV replication at new sites within the viral life cycle. These new drugs may improve clinical outcomes in persons infected with multidrug-resistant HIV. This review addresses the epidemiology and biological mechanisms of HIV drug resistance and the new approaches to detect and combat HIV drug resistance.

Keywords: Antiretroviral therapy, HIV drug resistance, HIV genotyping

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Introduction

Death rates due to human immunodeficiency virus (HIV) have markedly decreased in regions of the world that have full access to antiretroviral drugs. Currently, there are six classes of antiretroviral drugs that inhibit HIV replication at multiple different sites in the viral life cycle [1]. However, in the face of this advance, there is concern about the development and transmission of drug-resistant HIV strains. HIV drug resistance occurs with every antiretroviral agent. The development of resistance limits the efficacy of all antiretroviral drugs [2,3]. Drug resistance can lead to treatment failure and is associated with increased mortality [4–7]. Therapy for persons infected with multidrug-resistant HIV can be complicated and often leads to difficult patient management issues for clinicians. Furthermore, HIV-infected persons with resistant strains have been shown to continue HIV risk behaviours and to transmit resistant strains to newly infected persons [8]. This article addresses the epidemiology and biological mechanisms of HIV drug resistance and the new approaches to detect and treat drug-resistant HIV strains.

HIV Drug Resistance Dynamics

In an untreated HIV-infected person, approximately ten billion viruses are produced each day, and 100 million new cells are infected [9,10]. The poor fidelity of the HIV reverse transcriptase allows for random mutations with each round of HIV replication [9]. HIV has a high mutation rate, such that, theoretically, every possible single-base mutation can occur within the virus each day [9,10]. These evolutionary characteristics make HIV highly responsive to selection pressure from drugs that are not fully suppressive of viral replication. If an antiretroviral regimen does not fully control HIV replication, drug pressure will lead to the selection and preservation of viral variants with increasingly reduced drug susceptibilities [2]. Continued viral replication in the presence of drug pressure allows for the progressive accumulation of mutations that can lead to increased resistance [2,11]. Some antiretrovirals require only a single point mutation to have high-level drug resistance, whereas others require multiple point mutations [3,11]. The number of mutations required to confer resistance contributes to the genetic barrier to resistance [2,3,11]. Resistant variants in the blood can be replaced by wild-type populations when drug pressure is not

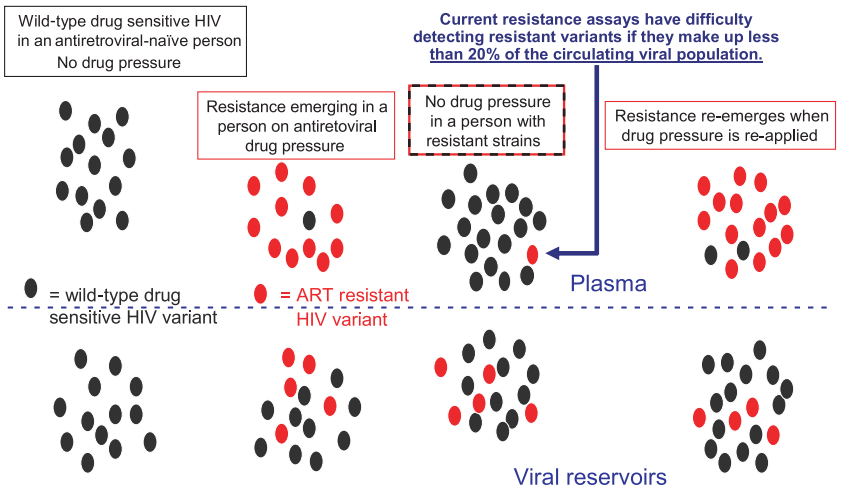

Fig. 1. Illustration of the emergence and archiving of drug-resistant human immunodeficiency virus (HIV) variants. A drug-resistant viral strain that is the dominant variant when drug pressure is present can become a minority (low-abundance) viral variant in the blood when drug pressure is removed. In this clinical situation, the currently available clinical genotypic resistance assays cannot detect these resistant variants when they fall below a level of *c.*20% of the circulating viral population. In an HIV-infected person, if an antiretroviral regimen is used which the minority viral variant is resistant to, the variant can multiply under the drug pressure and rapidly re-emerge, causing treatment failure. ART, antiretroviral therapy.

present. This results from a reversion to a wild-type viral genotype from variants with resistance mutations or the outgrowth of wild-type virus from viral reservoir sites (Fig. 1). However, resistant variants can seed reservoir sites (e.g. latent infected T-cells) and re-emerge if that drug is used again (Fig. 1).

Epidemiology and transmission of drug-resistant HIV strain

The emergence of HIV drug resistance in persons on therapy and the transmission of resistant HIV strains to newly infected persons are now major public health problems. Transmission of drug-resistant HIV to newly infected persons is a function of the type and the frequency of HIV transmission risk behaviours, the penetrance of antiretroviral drugs in a population, the prevalence of drug resistance in those engaging in risk behaviour, and the stability and transmissibility of resistant strains.

HIV-infected persons harbouring drug-resistant strains have been shown to transmit resistant HIV through high-risk HIV transmission behaviours (unprotected sex or the sharing of needles). Our group investigated the prevalence of drug resistance in HIV-infected persons under medical care who continued to engage in high-risk HIV transmission behaviours [8,12]. Unprotected sexual behaviour was reported by 45% of HIV-infected sexually active patients at some point during an approximately 2-year study period. Of these persons engaging in unprotected sexual events, 31% had HIV drug resistance at the time of a sexual risk event (*c.*13% with multidrug resistance) [13]. As with other sexually transmitted diseases, there was substantial and complex variation in the distribution of unprotected sexual events and in the detection of resistance over time. These data demonstrated the importance of ongoing risk reduction strategies for individuals undergoing clinical care for HIV[13].

Burden of drug resistance in HIV populations

In one of the largest HIV drug resistance surveys ever performed in the USA, the estimated prevalence of HIV drug resistance among an adult HIV-positive population that had a detectable HIV viral load was *c.*75%, with 48% harbouring multidrug-resistant strains [14]. This US survey covered a time period during which many among the infected population had been exposed to the inferior, early antiretroviral regimens commonly used in the mid-1990s. However, many of these HIV-infected persons may have been able to achieve viral suppression with newer antiretroviral regimens. Recent data suggest that the burden of resistance may be declining in resource-rich countries as newer initial antiretroviral therapy regimens achieve better results [15,16]. It is still sobering

that the burden of resistance among HIV populations can be significant, and this underscores the importance of the continued development of new antiretrovirals and new strategies to treat drug-resistant strains [17].

What will be the burden of resistance in resource-poor countries? Often, in resource-poor countries, the identification of a person failing an initial antiretroviral regimen is based on clinical or immunological monitoring [18]. Viral load monitoring, which would allow the early capture of viral escape, is not widely available in these regions, owing to cost and availability. This inability to detect resistance at an early stage, thus prolonging the detection of regimen failure, has raised the concern that more persons may have multiclass-resistant strains, over time, than if such monitoring were available.

Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens are the most commonly used first-line therapies in both resource-rich and in resource-poor countries. The ability to co-formulate three drugs (two nucleoside reverse transcriptase inhibitors (NRTIs) plus an NNRTI) into a single pill and the excellent virological response rates with these combinations have led to their preferred use as first-line therapy in many programmes. Persons failing these first-line antiretroviral regimens can become resistant to a single class or two classes of antiretrovirals. The likelihood of developing multidrug-resistant strains depends on the regimen used and the time for which a person is left on a failing regimen. In the minority of patients who fail an NNRTI-based regimen, resistance to both the NNRTI and nRTI drug classes can occur, resulting in a person harbouring multidrug-resistant strains [7]. It is possible to construct an antiretroviral salvage regimen in these patients when there is broad access to other antiretroviral classes [7]. Unfortunately, this is not an option in all regions of the world. Thus, over time, the burden of resistance in treated populations in many of the developing countries will probably increase.

HIV drug resistance in the newly infected person

The prevalence of drug-resistant strains in newly HIV-infected persons depends on the survey period and region of the world investigated. The general estimates are that in the parts of the world where antiretrovirals have been widely available for almost 20 years, the rates are approximately 10% (8–15% in the USA and *c.* 10% in Europe) [17,19,20]. In other parts of the world where antiretroviral drugs have been available for only a limited time, the prevalence is lower, often <5% [21]. Over time, as antiretroviral 'roll-out' programmes enroll increasing numbers of HIV-infected individuals, the likelihood of the transmission of drug-resistant strains will increase. The WHO recommends that HIV drug resistance surveillance be part of antiretroviral treatment programmes [21]. Surveillance for emergent, and transmitted, drug-resistant strains in these populations will help instruct the programmes and assist in the development of strategies to prevent the development and transmission of drug-resistant strains [21].

The transmission of HIV strains that are resistant to first-line therapy options in developing countries may disproportionately affect these communities. These regions have only limited options for second-line antiretroviral regimens, as many new antiretroviral drug classes that have activity against drug-resistant HIV strains are not readily available, because funds to purchase these newer agents are lacking. Thus, the rates of response to salvage antiretroviral regimens in these regions may not be as robust as those in parts of the world that have access to the full arsenal of antiretroviral drug classes.

Detection of HIV drug-resistant strains

It is standard practice to monitor HIV drug resistance using either genotypic or phenotypic resistance assays. The use of resistance assays can instruct drug selection, help in patient management, and improve therapy outcomes [1]. However, a major limitation of commercial resistance assays is their inability to detect low-abundance resistant variants that exist as a small portion of the viral population when there is no antiretroviral drug pressure. Standard resistance assays used in the clinic reliably detect resistant variants only if they make up at least 20% of the circulating viral population [1]. Recent data from multiple groups suggest that resistant viral variants that make up as little as 1% of the viral population in a person are clinically important, as they can rapidly grow under drug selection pressure [22,23]. In these studies, low-abundance resistant variants were found in both acutely and chronically infected populations, and the detection of these previously occult resistant variants predicted subsequent treatment failure [22,23]. Thus, new resistance technologies are needed for the clinic to screen for all types of low-abundance resistant variants. Such assays could have greater clinical utility, improve patient care, and might prove valuable in predicting virological responses to new antiretroviral regimens. A major area of investigation in the HIV resistance field is how best to improve the existing assays to achieve this goal.

Antiretroviral agents to treat drug-resistant strains

Recently, there have been multiple new antiretroviral agents approved for use in persons infected with drug-resistant HIV. Some of these agents have unique mechanisms of action and inhibit the virus at new sites in the viral life cycle. This advance has allowed clinicians to construct new regimens for persons with multidrug-resistant HIV that have resulted in excellent virological suppression rates [1]. The recently approved antiretroviral agents include new protease inhibitors (darunavir and tipranavir), an NNRTI with activity against drug-resistant HIV strains (etravirine), and antiretroviral classes that inhibit the virus at new sites of the viral life cycle, CCR5 inhibitor (maraviroc) and an integrase inhibitor (raltegravir) (Fig. 2).

The antiretroviral development process has not been synchronous, and the approval of new antiretrovirals was often spread out over many months to years. This staggered release of antiretrovirals led to the use of new agents as functional monotherapy in many patients. New antiretroviral agents were often added to a failing regimen as clinicians were pressed to prevent further immunological deterioration in a person with advanced HIV disease. A single new drug addition to a failing regimen often led to transient virological responses with subsequent therapy failure and the development of even broader multiclass resistance (resistance to the recently added antiretroviral agent in addition to the pre-existing resistance). This clinical practice led to the development of multidrug-resistant HIV strains in many persons.

However, the HIV field has now reached a point in clinical care where, if a person develops multidrug-resistant HIV after initial treatment with an NRTI + NNRTI or NRTI + PI/r (protease inhibitor boosted by ritonavir)-based regimen, a clinician can construct a second-line or third-line antiretroviral regimen that contains two to three new agents with different mechanisms of activity. These new combinations can yield excellent results against multidrug-resistant HIV [1]. Hopefully, this new capability will lead to a lower resistance burden in HIV-infected populations over time (at least in populations that have full access to all antiretroviral drug classes). An important issue for the field will be to bring these newer agents to all who are in need, especially in resource-poor regions, faster than has been done in the past.

Conclusion

Antiretroviral therapy has dramatically reduced HIV-related mortality. There is an ongoing rapid scale-up of access to antiretroviral therapy in the regions of the globe where HIV-infected populations are in great need. This may lead to the emergence and transmission of drug-resistant strains of HIV, an important problem that we have already witnessed in parts of the world that have had long-standing access to antiretrovirals. The transmission of drug-resistant HIV is an important public health issue in all regions of the world. HIV drug resistance surveillance programmes (such as the WHO HIVDR Program) are needed to ensure the efficacy of antiretroviral therapy programmes and to help direct the choice

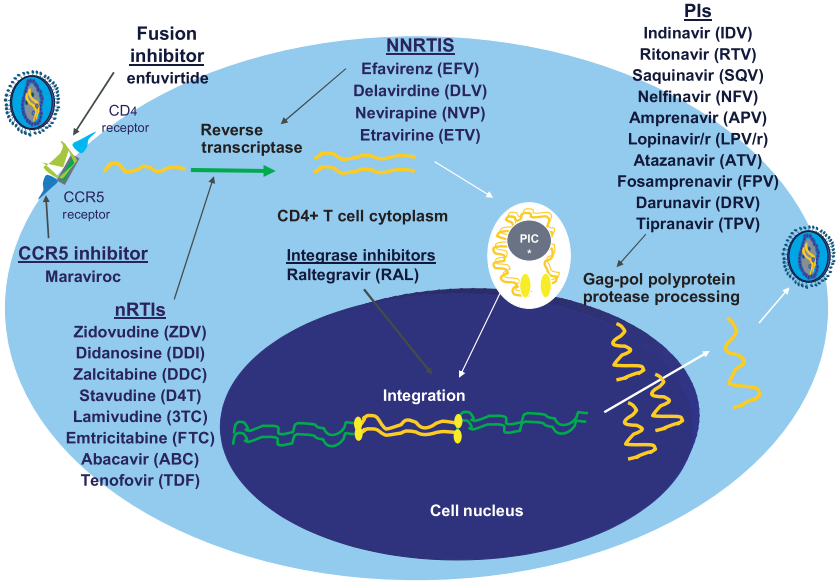

Fig. 2. Antiretroviral classes/drugs and their site of activity: nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs); non-nucleoside reverse transcriptase inhibitors (NNRTIs); protease inhibitors (PIs); fusion inhibitor; CCR5 inhibitor; integrase inhibitor; *pre-integration complex (PIC).

of drugs and intervention programmes. Furthermore, new resistance technologies are needed to better monitor low-abundance drug-resistant HIV variants, as these variants can lead to treatment failure. The availability of new antiretroviral drug classes that have activity against drug-resistant strains should improve the clinical outcomes in those infected with multidrug-resistant strains of HIV. Global access to these important new agents will be an important issue for the field.

Transparency Declaration

MJK has received grant support from Merck, Tibotec and Boehringer-Ingleheim. MJK has received royalties from a patent owned by Stanford University for some HIV diagnostic tests. Yale has submitted patent applications on other HIV genotyping assays developed by MJK. MJK has been a consultant for Stanford University, Merck and Shering-Plough Research Institute, and has received honoraria and speaker fees, including reimbursement for travel and accommodation expenses, from Abbott and 454 Life Sciences/Roche.

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