Commentary

Transmitted resistance to HIV integrase strand-transfer inhibitors: right on schedule

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Transmitted drug resistance (TDR), the primary acquisition of an HIV variant already resistant to antiretrovirals, affects approximately 15% of all new infections in the United States.
Historically, from the time initial agents in the reverse transcriptase, protease and entry inhibitor classes were introduced, it took 3–5 years before the first case reports of TDR appeared. With the description of the first two cases of transmitted integrase stand-transfer inhibitor resistance, it is only a matter of time before the prevalence of TDR affecting this newest antiretroviral class reaches a level warranting baseline resistance testing for all patients entering care.

Introduction

Of the estimated 56,000 individuals with new HIV infections each year in the United States [1], approximately 8,000 will acquire viruses resistant to at least one antiretroviral (ARV) at baseline [2]. For these patients, their care providers and public health, the presence of transmitted drug resistance (TDR) poses a number of challenges.

Resistant variants persist for long periods in both the blood [3,4] and the genital tract [5], increasing the potential for forward transmission among the undiagnosed or untreated. Individuals with TDR seem to have steeper declines in $CD4^+$ T-cell counts in the first year after infection [6], which may affect immunological recovery later. Once engaged in HIV care, pre-existing resistance restricts available first-line ARV options and may force providers to select alternative regimens with less favourable dosing intervals or side effect profiles. Adherence may suffer as a result, placing patients at increased risk for accumulating additional resistance mutations over time. Finally, although patients with resistant viruses are benefitting from new ARV classes introduced over the past several years, the current ARV drug development pipeline is relatively limited.

One of the new products from that pipeline is raltegravir, the prototype integrase strand-transfer inhibitor (InSTI) that earned US Food and Drug Administration (FDA) approval in 2007. Its safety profile, tolerability and potency when paired with tenofovir/emtricitabine [7] prompted the inclusion of this combination as a preferred first-line regimen in the US Department of Health and Human Services (DHHS) adult HIV treatment guidelines in 2009 [8]. This decision is further supported by studies demonstrating an extremely low prevalence of mutations associated with raltegravir resistance in treatment-naive patients [9,10]. Unlike the recommendation to pursue baseline genotypic resistance testing of reverse transcriptase (RT) and protease, the DHHS guidelines specifically noted that pretreatment integrase resistance testing was not necessary – at least not yet [8].

With the first two documented cases of transmitted InSTI resistance reported in this issue of *Antiviral Therapy* [11,12], it is only a matter of time before that recommendation changes. But how soon after the introduction of a new ARV class can one expect to see significant circulating resistance? And just how much time do we have before the prevalence of transmitted InSTI resistance reaches a threshold that makes pretreatment testing necessary? Some historical perspective may help us answer these questions (Table 1).

The first published report of TDR came in 1993, when a young man who presented with acute HIV infection was started on single-agent zidovudine but failed to have any significant response following 3 months of treatment. After it was learned that one of his likely source partners was receiving zidovudine, retrospective analysis of pretreatment samples demonstrated the presence of T215Y/F mutations in RT, conferring

Table 1. Date of first clinical trial publication, US FDA approval and initial report of TDR for selected antiretrovirals

Year	Antiretroviral class and agent[a]					Event
	NRTI	NNRTI	PI	EI	InSTI	
1986	ZDV	–	–	–	–	Yarchoan *et al.* [33] publish first clinical trial
1987	ZDV	–	–	–	–	FDA approval [34]
1993	ZDV	–	–	–	–	Erice *et al.* [13] report TDR
	–	NVP	–	–	–	Cheeseman *et al.* [17] publish first clinical trial
1995	–	–	SQV	–	–	Kitchen *et al.* [21] publish first clinical trial
	–	–	SQV	–	–	FDA approval [34]
1996	–	NVP	–	–	–	FDA approval [34]
1997	–	NVP	–	–	–	Imrie *et al.* [18] report TDR
1998	–	–	SQV	–	–	Hecht *et al.* [20] report TDR
2002	–	–	–	ENF	–	Kilby *et al.* [35] publish first clinical trial
2003	–	–	–	ENF	–	FDA approval [34]
2006	–	–	–	–	RAL	Markowitz *et al.* [36] publish first clinical trial
2007	–	–	–	–	RAL	FDA approval [34]
	–	–	–	ENF	–	Peuchant *et al.* [37] report TDR
2010	–	–	–	–	RAL	Young *et al.* [11] and Boyd *et al.* [12] report TDR

EI, entry inhibitor; ENF, enfuvirtide (T-20); FDA, US Food and Drug Administration; InSTI, integrase strand-transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RAL, raltegravir; SQV, saquinavir; TDR, transmitted drug resistance; ZDV, zidovudine.

resistance to the drug [13]. Six years of widespread zidovudine monotherapy following its FDA approval in 1987 led to a high prevalence of resistance among potential transmitters, and up to 10% of seroconversions harboured T215 mutations in select cohorts between 1988 and 1994 [14]. Within a decade of the introduction of the class, TDR involving nucleoside reverse transcriptase inhibitors (NRTIs) was stably high and ranging between 9 and 42% [15,16].

Only 4 years elapsed between initial clinical studies in 1993 [17] of nevirapine, the first non-nucleoside reverse transcriptase inhibitor (NNRTI), and the first report of NNRTI-associated transmitted resistance in 1997. The HIV-uninfected male partner of a patient on zidovudine plus nevirapine dual therapy developed symptoms of primary HIV infection and was found to have K70R, A98G and Y181C mutations in RT, identical to those in the donor [18]. By 2000, the prevalence of NNRTI-associated mutations among treatment-naive patients reached 13% [19].

Protease inhibitor (PI) transmitted resistance trailed the introduction of the class by only 3 years; primary infection with HIV resistant to NRTIs and PIs was initially described in 1998 [20]. The source patient in that case report had an extensive prior treatment history, including all available NRTIs and PIs (saquinavir, ritonavir and indinavir). It took 5 years from saquinavir's introduction in 1995 [21] to reach a PI TDR prevalence of 8–9% [19,22].

It is important to consider, however, that the population dynamics of resistance today are arguably very different from what they were at the time these studies demonstrated such rapid increases in the frequency of TDR. Before the advent of HAART, incompletely suppressive mono- or dual-therapy regimens left large portions of the HIV-infected population living chronically with detectable, drug-resistant viraemia. Given the relationship between viral load and the likelihood of transmission [23], this large 'reservoir' of circulating resistance supported multiple introductions of ARV resistance into the uninfected population over time. With the effective and durable virological suppression afforded by contemporary HAART regimens, the majority of patients on therapy have low or undetectable viral loads – leading to a broadly reduced risk of forward transmission. Longitudinal data on the effect of lowered 'community' viral load on HIV incidence support this hypothesis [24,25], as do trends in observed TDR prevalence over time. Levels of primary resistance appear to have peaked between 2000 and 2002, with a slight decrease and subsequent stabilization to the present day [26,27].

That the first cases of transmitted InSTI resistance come only 3 years after raltegravir's FDA approval is therefore somewhat disconcerting. Certainly this short time span could be artifact; broader availability and application of routine pretreatment resistance testing and greater awareness of TDR could have led to heightened vigilance and more aggressive screening. But it is also possible that its appearance reflects our ongoing failures in secondary prevention efforts among people living with HIV – especially the treatment-experienced. Clear associations exist between poor adherence and transmission risk behaviours [28,29],

and multiple studies implicate small numbers of highly risky patients with resistant viruses as potentially being responsible for a disproportionately large amount of TDR [30–32].

The current reports of transmitted InSTI resistance by Young *et al.* [11] and Boyd e*t al.*, [12] are important milestones as we advance toward a better understanding of HIV resistance and the optimal approach to patients entering care. We are now officially on the clock, waiting for the point at which the prevalence of integrase mutations among treatment-naive patients rises to a level that warrants routine baseline resistance testing. In the meantime, these cases clearly support the addition of InSTI resistance testing for patients presenting to care with higher-than-expected baseline levels of RTI and PI mutations, and for those whose risk histories place them in contact with source patients having ARV treatment experience.

With the history of TDR as a guide, the next several years offer us the opportunity to both actively monitor for increasing InSTI resistance and to improve our understanding of the epidemiology of TDR. Despite the large and growing number of papers on TDR prevalence worldwide, precious few make any attempt to determine what factors are associated with the acquisition of resistant HIV. If we were able to uniformly collect sociodemographic and behavioural data on cases prospectively, we might parlay those findings into effective prevention messages designed to reduce the incidence (and, eventually, the prevalence) of transmitted resistance.

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