

Possible Role of Integrase Inhibitors in the Management of Untreated HIV-Infected Subjects in Intensive Care Units

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Abstract

The introduction HIV integrase strand transfer inhibitors may help reduce the risk of acquiring the infection by the operators as well of developing complications by the patients, in case of admission of untreated HIV-1-infected subjects with potentially dangerous viremia, suppressing plasma HIV RNA concentrations by 10 folds every 3 days.

Keywords: Integrase inhibitors; Viral replication; Intensive care

Introduction

The World Health Organization (WHO) target to help end the Acquired Immuno Deficiency Syndrome (AIDS) epidemic is known as the “90-90-90” strategy [1]. This means that by the end of the year 2020, 90% of all people living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy and 90% of this therapy will have viral suppression [1]. This means that Member States of the WHO should adopt a ‘test and treat’ strategy, which is often not the case at present. Therefore, the first step of the chain, to diagnose 90% of all HIV-infected subjects, is still far from being achieved and subjects presenting with AIDS symptoms or with less than 200 CD4+ T-cells/mm³ and uncontrolled viral replication, unaware of their condition, are still admitted in hospital, with proportions up to 47% of new diagnoses [2,3]. Other subjects receive diagnosis and know their infection, but either refuse to face it or get tired of medicines, visits, side effects and do not undergo follow-up nor take medications, at least until some disease brings them to hospital.

Risk for health care workers

Patients with uncontrolled viral replication potentially pose a threat to healthcare workers. An analysis performed by the US CDC as of December 31, 2013 has retrieved 58 cases of occupational HIV infection in health care workers and 150 possible transmissions, but only one confirmed case had been reported after 1999 [4]. However, in other countries and in other hospital settings rates may be higher, ranging from 2.4 to 24 cases per million medical procedures [5]. At least one needle stick injury occurs in 20% of anesthesiologists in a 3 month work period [6]. Wearing double gloves reduces contamination of the skin by body fluids from the patient to the surgical team [7], but again this is not the rule everywhere and in some parts of the world glove stocks may often be depleted. The risk of infection associated with the exposure of mucous membranes to the HIV-infected blood is 0.09% [8]. The risk of HIV transmission through body fluids such as urine, sputum, feces, vomits, nasal secretions, sweat, and tears is low or absent if they do not contain visible blood [9].

Post-exposure prophylaxis (PEP)

Once an injury has occurred to the health care worker, causing direct contamination with infected body fluids from a subject who has uncontrolled HIV-1 replication the health care worker should start as soon as possible, within 48 h, post-exposure prophylaxis, taking

for 28 days a complete antiretroviral regimen and then checking HIV serostatus until the third or sixth month [10,11].

The Centers for Disease Control and Prevention recommend tenofovir diisoproxil fumarate (TDF)/emtricitabine plus twice-daily raltegravir (RAL) or once-daily dolutegravir (DTG) [12]. However, when the source of contamination is a subject who has a history of documented selection of genotypic mutations, other specific regimens are used. The Italian guidelines, given the absence of evidence of occupational transmission of HIV-1 in subjects who have achieved undetectable viremia, do not suggest proposing PEP in such cases, although if required by the health worker who feels unsecure PEP may be offered [11]. The use of PEP however is not as frequent as it should, especially in high-risk settings, as some reports dramatically point out [13].

Risks for the patients

HIV infection *per se* is not a contraindication to surgery and since several years HIV-infected patients have even undergone transplants of solid organs and bone marrow [14,15] and even ExtraCorporeal Membrane Oxygenation (ECMO) [16]. However, 3-5 year survival rates in HIV-HCV co-infected subjects are lower as compared to the Hepatitis C Virus (HCV) monoinfected population, due to higher prevalence of severe infections. In a retrospective study of surgical outcomes in 332 HIV- infected and matched HIV-non infected patients from the Kaiser Permanente Medical Care Program showed that the HIV-infected patients had a higher incidence of postoperative pneumonia and higher 12-month mortality, although other operative outcomes were comparable for HIV-infected and HIV-non-infected patients. Viral suppression to fewer than 30,000 copies/mL reduced surgical complications [17]. A smaller study from South Africa on patients undergoing surgery or drainage of sepsis on the contrary has

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not found an impact on the surgical outcome by HIV serostatus nor CD4 T-cell counts [18]. However, in their cohort, drainage of infectious foci was more common in HIV-infected subjects.

Viral dynamics of HIV-1 in plasma after the initiation of an integrase inhibitor-containing regimen

The class of integrase strand transfer inhibitors (INSTI) at present comprises two unboosted compounds, DTG and RAL, and one that is included in a fixed dose combination (FDC) with a booster, elvitegravir (ELV). DTG and RAL have showed to cause an extremely rapid HIV-1 RNA decay in blood after treatment initiation, with a 1a slope reduction of about 1 log₁₀ HIV-1 RNA copies/mL every 3 days [19-21]. This means that after only 3 days of therapy a subject starting with 300,000 HIV-1 RNA copies/mL, a fairly high level of replication would drop below the threshold for increased risk of surgical complications, according to the Kaiser Permanente study. After 12 days of therapy the subject may have gone below the threshold of infectious risk to the health workers, according to the Italian Guidelines for PEP (Figure 1). ELV-related effect has been less studied and at different doses and with a different booster than the commercially available formulations in the Gilead Study 183-0101 [22], however a 1 log₁₀ decay has been observed in all subjects (n=40) at day 10 and a 2 log₁₀ decay in about 50%.

Factors that may reduce the efficacy of INSTIs: Adherence, drug-drug interactions and genotypic resistance

The main barriers to success for antiretroviral therapy are the patient's adherence, the presence of drug-drug interactions and the presence of resistance mutations.

In any ward adherence can be readily addressed by the health care workers with controlled daily administration.

DTG and RAL have minimal interactions with other drugs, while the ELV-containing FDC has a similar profile to protease inhibitors, boosting many companion drugs. DTG AUC decreases by 39% if co-administered with calcium carbonate and by 54% with

ferrous fumarate in fasting conditions. Taking DTG 2 h before or 6 h after these minerals or with a high-fat meal effectively counteracts such effect [23]. The same effect results from the intake of antacids [24]. Concomitant administration of rifampicin, carbamazepine or tipranavir (TPV) reduces DTG C_{min} by ≥ 75%, requiring doubling the dose of DTG [25]. Simultaneous administration of calcium carbonate antacid with RAL resulted in 32% reduction in C_{12hr} and 55% reduction in AUC. Simultaneous administration of magnesium/aluminum with RAL resulted in 63% reduction in C_{12h} and 49% reduction in AUC. Administration of magnesium/aluminum either 2 h before or 2 hours after RAL resulted in 57% reduction in C_{12h} and 51-30% reduction in AUC, so the distance should be either 6 h before or 4 h later [26].

The possibility that the chosen antiretroviral regimen may be hampered by acquired resistant HIV-1 strains depends on the behaviour though which the patient had acquired the infection [27] and the rates of transmitted drug resistance in the HIV-infected population in that country.

The global prevalence of transmitted resistance to INSTIs is minimal with no demonstrated effect to date on DTG [28] and transmitted resistance to nucleoside analogues, the backbone of triple therapies, is particularly low in developing countries although and adequate surveillance system has still to be set [29]. DTG has a high genetic barrier, so that at least two mutations need to be transmitted to reduce its' efficacy, while RAL is more affected, and once a key mutation is present, tends to select accumulating mutations with progressive reduction in antiviral activity [30,31].

Practical implications of early treatment with an integrase inhibitor

The decision to treat immediately a patient with DTG or RAL must be preceded by the collection of plasma for HIV-1 quantitation and genotypic resistance testing, but the results can be acknowledged later. It takes generally two days for an RT-PCR HIV-1 RNA test to generate results and 10 days for a genotypic resistance test performed in urgency.

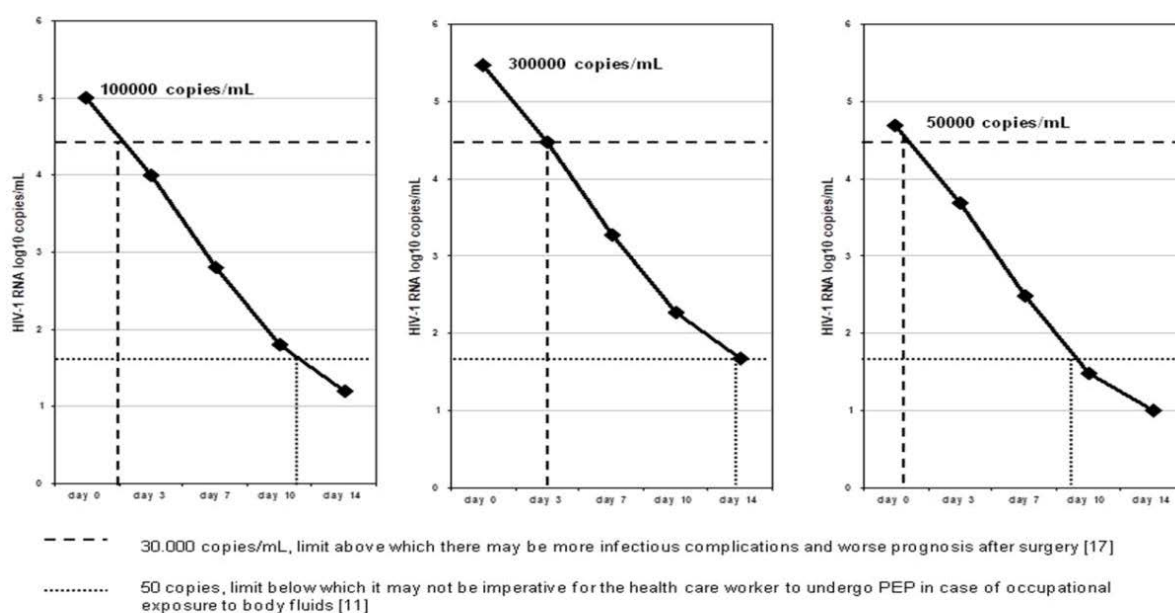


Figure 1: HIV-1 RNA decays dynamics in plasma after starting raltegravir or dolutegravir-based regimens with different initial viral concentrations.

Often a patient in an Intensive Care Unit is not able to swallow. In this case the preferred backbone would probably be chosen among abacavir, emtricitabine, lamivudine and tenofovir either using the liquid formulations, which are commercially available or crushing the tablets of the separate components or even the Truvada™ tablet, which is allowed [32,33]. Also DTG tablets may be split into halves followed by immediate ingestion of both halves or crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately [34]. Raltegravir cannot be crushed; however it is also available as oral suspension which should be administered within 30 min of mixing.

In case of patients with uncontrolled HIV-1 replication whose viral strains harbours resistance mutations other compounds that may be given crushed or in liquid formulation include atazanavir, darunavir, didanosine, fosamprenavir, lopinavir/ritonavir, maraviroc, nevirapine, ritonavir, saquinavir, stavudine and zidovudine [34].

Conclusion

Since dolutegravir and raltegravir-based regimens offer the chance of rapidly controlling viral replication in untreated HIV-infected subjects, reducing the risk of acquiring infection through occupational exposure and improving the patient's response to surgery and ventilation, treatment should be started as soon as possible, having excluded the possibility of drug-drug interactions as well as the presence of previously documented HIV drug resistance.

Implications for Nursing

Rapidly abating HIV-1 replication renders daily care to HIV-infected subjects safer, however the level of awareness and prudence should not be lowered, as the possibility of an underlying drug-resistant strain cannot be 100% excluded and the patients' immune recovery takes longer time than viral suppression. HIV-infected subjects therefore have still to be considered more vulnerable, unless on stable suppressive therapy since several years.

Finally, for countries with endemic or imported HIV-2 infection, or in case of documented HIV-2 infection, it should be reminded that the data presented have been obtained on HIV-1, although this kind of drugs may also have some effect on HIV-2 [35].

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