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Overview of HIV molecular epidemiology among People who Inject Drugs in Europe and Asia

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Abstract

HIV strains continuously evolve, tend to recombine and new circulating variants are being discovered. Novel strains complicate efforts to develop a vaccine against HIV and may exhibit higher transmission efficiency and virulence, and elevated resistance to antiretroviral agents. The United Nations Joint Programme on HIV/AIDS (UNAIDS) set an ambitious goal to end HIV as a public health threat by 2030 through comprehensive strategies that include epidemiological input as the first step of the process. In this context, molecular epidemiology becomes invaluable as it captures trends in HIV evolution rates that shape epidemiological pictures across several geographical areas.

This review briefly summarizes the molecular epidemiology of HIV among people who inject drugs (PWID) in Europe and Asia. Following high transmission rates of subtype G and CRF14_BG among PWID in Portugal and Spain, two European countries, Greece and Romania, experienced recent HIV outbreaks in PWID that consisted of multiple transmission clusters including subtypes B, A, F1 and recombinants CRF14_BG and CRF35_AD. The latter was first identified in Afghanistan. Russia, Ukraine and other Former Soviet Union (FSU) states are still facing the devastating effects of epidemics in PWID produced by A_{FSU} (also known as IDU-A), B_{FSU} (known as IDU-B), and CRF03_AB. In Asia, CRF01_AE and subtype B (Western B and Thai B) travelled from PWID in Thailand to neighboring countries. Recombination hotspots in South China, Northern Myanmar, and Malaysia have been generating several intersubtype and inter-CRF recombinants (e.g. CRF07_BC, CRF08_BC, CRF33_01B etc.) increasing the complexity of HIV molecular patterns.

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Conflict of Interest.

The authors declare that they have no conflict of interest.

Keywords

HIV; molecular epidemiology; subtypes; PWID; drug injecting

1. Introduction

In 1981, unexpected cases of Kaposi sarcoma and Pneumocystis carinii (now known as jirovecii) pneumonia were diagnosed among young men who have sex with men (MSM) (Centers for Disease Control, 1981a, 1981b; Gottlieb et al., 1981). The United States (US) Centers for Disease Control and Prevention (CDC) carried out detailed investigations and soon defined the Acquired Immune Deficiency Syndrome (AIDS) hinting also at a viral etiology of the new disease (Centers for Disease Control, 1982a, 1982b). Human Immunodeficiency Virus (HIV), which causes AIDS, was eventually discovered in 1983 (Barré-Sinoussi et al., 1983; Gallo et al., 1984) but the scientific community soon realized that HIV had been spreading globally before the initial recognition of AIDS in the US. As a matter of fact, a stored sample collected in 1959 in Belgian Congo (now Democratic Republic of the Congo) tested positive for HIV (Nahmias et al., 1986; Zhu et al., 1998) and molecular investigations have shown that HIV was the result of cross-species transmissions from different primates that had taken place long before the first diagnoses (Gao et al., 1999; Keele et al., 2006; Sharp and Hahn, 2011; Van Heuverswyn et al., 2006). The most recent ancestor of the pandemic strain was probably circulating in human populations in Central Africa early in the 20th century (Faria et al., 2014; Korber et al., 2000; Worobey et al., 2008).

The toll of HIV has been high with millions of HIV infections and HIV-related deaths since the early 1980s (Faria et al., 2014; Sharp and Hahn, 2011). However, considerable progress has occurred over the years, which transformed HIV from a lethal disease to a chronic condition. Combinations of potent antiretroviral drugs (antiretroviral treatment - ART) in simplified regimens have significantly reduced morbidity and mortality, and people infected today can anticipate an almost normal life expectancy (Mills et al., 2011; Nsanzimana et al., 2015; Samji et al., 2013; The Antiretroviral Cohort Collaboration, 2008). Following intensified efforts by the World Health Organization (WHO) and the United Nations Joint Programme on HIV/AIDS (UNAIDS), around 17 million people worldwide were on ART in 2015 (UNAIDS, 2016, 2015). In addition, treatment as prevention (TasP) (Cohen et al., 2011a) and pre-exposure prophylaxis (PrEP) (Grant et al., 2010; McCormack et al., 2015; Molina et al., 2015) are promising prevention approaches added to the existing arsenal of effective tools (Giannou et al., 2015) and UNAIDS has thus set an ambitious goal to end the HIV epidemic, as a public health threat, by 2030 (UNAIDS, 2015).

The first important element of a comprehensive strategy to contain HIV transmission and reach UNAIDS targets is public health authorities and other groups in each locale to understand their epidemic (WHO, 2015). Epidemiological input from HIV/AIDS reporting systems, biological surveillance, and behavioral surveys is necessary to get a deep understanding of local epidemics that could then help design, implement, and evaluate appropriate prevention measures (WHO and UNAIDS, 2013). In this context, molecular

studies become invaluable as they shed light on parameters that traditional epidemiological techniques fail to capture.

This review summarizes evidence on circulating HIV-1 subtypes in people who inject drugs (PWID) in Europe and Asia. This geographical area includes countries with past or recent PWID-related outbreaks (Nikolopoulos et al., 2015a), countries with mega-epidemics in PWID such as Ukraine, Russia, China, and Malaysia (Wolfe et al., 2010), and hotspots of ongoing recombination processes (Lau and Wong, 2013).

2. Molecular Epidemiology

HIV-1 and HIV-2 comprise two distinct types of HIV. HIV-2 is classified in groups (A to G) and one recombinant (HIV2_CRF01_AB), and is more closely related to Simian Immunodeficiency Viruses (SIV) isolated from sooty mangabeys (Clavel et al., 1986; Gao et al., 1992; Ibe et al., 2010; Sharp and Hahn, 2011). HIV-2 is mostly concentrated in West Africa although it has been detected in other geographical settings, especially in those with historical and political ties to West Africa (Campbell-Yesufu and Gandhi, 2011; Soriano et al., 2000). Between 1 and 2 million people live with HIV-2 in West Africa but both its incidence and prevalence show decreasing trends probably because the transmission efficiency of HIV-2 is lower than that of HIV-1 (Campbell-Yesufu and Gandhi, 2011; Tienen et al., 2010). HIV-2 is less pathogenic than HIV-1 with slower progression to advanced disease (Campbell-Yesufu and Gandhi, 2011). ART administration to the HIV-2 infected population is challenging and probably suboptimal (Ekouevi et al., 2014).

HIV-1 is the pandemic type and consists of 4 groups, M, N, O and P, each of which represent independent cross-species transmission events of SIV from chimpanzees (*Pan troglodytes troglodytes*) and gorillas (D'arc et al., 2015; Gao et al., 1999; Keele et al., 2006; Sharp and Hahn, 2011; Van Heuverswyn et al., 2006). Group N has been identified in very few cases accounting for approximately 0.1% of infections in Cameroon (Roques et al., 2004; Sharp and Hahn, 2011; Simon et al., 1998; Vallari et al., 2010), while Group O is limited to Cameroon and other adjacent countries having infected around 100,000 individuals (Charneau et al., 1994; D'arc et al., 2015; Gürtler et al., 1994; Peeters et al., 1997; Roques et al., 2002; Sharp and Hahn, 2011). Group P was discovered in 2009 and has been detected insofar in only two persons (D'arc et al., 2015; Plantier et al., 2009; Sharp and Hahn, 2011; Vallari et al., 2011).

Around 1960, Group M transitioned epidemiologically to a faster growth rate outpacing regional population growth and managed to spread globally (Faria et al., 2014). Group M strains are classified into nine genetically distinct subtypes (A-D, F-H, J, K), subsubtypes (A1, A2, F1, F2), circulating recombinant forms (CRFs) that have been detected in at least three epidemiologically unlinked individuals, and unique recombinant forms (URFs) (Peeters et al., 2013). Based on global estimates for 2000-2007, subtype B is dominant in Western and Central Europe, Australia and the Americas but represents around 11% of all circulating strains (Hemelaar et al., 2011; Takebe et al., 2008, 2004). Approximately half (48%) of the HIV-1 infected population carries subtype C, which is prevalent in southern Africa and India (Abecasis et al., 2013; Hemelaar et al., 2011; Takebe et al., 2008, 2004).

Almost all subtypes and most CRFs and URFs circulate in the Democratic Republic of the Congo and Cameroon where HIV probably originated (Hemelaar et al., 2011). Globally, A, G, D, CRF02_AG, and CRF01_AE account for 12%, 5%, 2%, 8%, and 5% of infections (Abecasis et al., 2013; Hemelaar et al., 2011). Geographical patterns are not stable and may change over time. The proportions of subtype A, CRF01_AE, and CRF02_AG have increased over time (Hemelaar et al., 2011). Although a biological effect on the different and changing estimates of subtypes prevalence is uncertain, previous research has found, for instance, that subtype A viruses had higher rates of heterosexual transmission and lower rates of disease progression than subtype D viruses in the Rakai district of Uganda (Kiwanuka et al., 2009, 2008). Changes in the distribution of HIV subtypes over time is certainly a complex and multifactorial phenomenon, and includes founder effects, population growth and mixing, migration and interconnectivity between geographical settings (Hemelaar et al., 2011). It should be noted that recent reviews suggest an even higher prevalence for subtype B and much lower for subtype C (Lau and Wong, 2013). Finally, new CRFs are continuously being discovered, especially in recombination hotspots in Africa, Southeast Asia, and South America (Lau and Wong, 2013). The current number of identified CRFs is 79 (http://www.hiv.lanl.gov/; assessed May 28th, 2016).

3. HIV transmission and epidemiology among PWID

An HIV infectee can pass the virus onto susceptible individuals usually through unprotected sexual intercourse, by sharing of injecting equipment, and vertically such as from infected mothers to children during pregnancy, at delivery, and through breastfeeding (Cohen et al., 2011b). The estimated risk of infection following needle/syringe sharing with an HIV positive individual is 0.63% and comes fourth after blood transfusion (92.5%), perinatal transmission (22.6%), and receptive anal intercourse (1.38%) (Patel et al., 2014).

A systematic review has calculated that approximately 16 (11-21) million people worldwide inject drugs. Of these, 4 (3-5) million are in East and Southeast Asia, 3.5 (2.5-4.5) million in Eastern Europe, 2.2 (1.6-3.1) million in Canada and the US, 2 (1.5-2.5) million in Latin America, 1.8 (0.5-3) million in Sub-Saharan Africa, and 1 (0.8-1.3) million in Western Europe (Mathers et al., 2008).

It is estimated that 36.7 million people were living with HIV in 2015 and more than half of them were in Sub-Saharan Africa, mostly infected through unprotected sexual intercourse (UNAIDS, 2016, 2015). Injecting drug use is responsible for nearly 10% of all HIV infections (Mathers et al., 2008; Strathdee and Stockman, 2010). Around 3 million (0.8-6.6) PWID are infected with HIV and most of them are in Eastern Europe (~1 million), in East and Southeast Asia (0.7 million), and in Latin America (0.6 million), while the rest are in Canada and the US (0.35 million), in Sub-Saharan Africa (0.2 million), and in Western Europe (0.1 million) (Mathers et al., 2008).

Management of HIV disease in PWID is challenging. PWID may also suffer from mental illness, co-infection with hepatitis B or C and tuberculosis is common, and they are at increased risk of experiencing drug overdose, violence, and incarceration (Kamarulzaman and Altice, 2015). Although not corroborated by some studies (Wood et al., 2008), drug

injectors seem to have suboptimal outcomes along the HIV continuum of care with heightened rates of AIDS and mortality, both overall and liver-related, following initiation of ART (Kamarulzaman and Altice, 2015; Larsen et al., 2010; Murray et al., 2012; Weber et al., 2015). Increased access to treatment, retention to care and adherence to ART, provision of integrated services, fighting stigma and discrimination, reform of harmful policies, and lack of hepatitis C co-infection can improve the outcome of HIV+ PWID (Braitstein et al., 2006; Kamarulzaman and Altice, 2015; Murray et al., 2012; Wolfe et al., 2010).

4. PWID in Former Soviet Union (FSU) states and molecular epidemiology of HIV

The collapse of Former Soviet Union was followed by economic instability, newly-established networks of drug trafficking, high unemployment rates, serious destruction of norms and values, intergenerational gaps, and youth alienation, which, in turn, contributed to increased rates of injecting drug use and a huge HIV epidemic among PWID (Friedman et al., 2009; Rhodes and Simic, 2005; Strathdee et al., 2006; United Nations Office on Drugs and Crime (UNODC), 2014). Heterosexual transmission of HIV has gradually been increasing and constitutes now the main route of HIV spread in Eastern Europe (European Centre for Disease Prevention and Control (ECDC)/World Health Organization (WHO), 2014). It is estimated that around 1.5 million people live nowadays with HIV in Eastern Europe and Central Asia, and more than 90% of them are in Russia and Ukraine (Bobkova, 2013). Molecular patterns of HIV spread among PWID in the region are shown in Figure 1.

Between the late 1980s and early 1990s, HIV diagnoses in FSU were rather limited, primarily representing sexually-acquired infections (mostly abroad) and nosocomial outbreaks affecting children in southern Russia, and were characterized by substantial molecular diversity (circulating strains included subtypes A-D, F, G, H, and some recombinants) (Bobkov et al., 1994, 2004a; Bobkova, 2013; Lukashov et al., 1995; Thomson and Najera, 2007). However, a big HIV epidemic among PWID started in Ukraine in the mid-1990s and was the result of two single introductions of sub-subtype A1 (called A_{FSU} or IDU-A) and subtype B (labelled here B_{FSU} or, as is widely known, IDU-B) (Bobkova, 2013; Nabatov et al., 2002). A_{FSU} that originated in Africa (Thomson et al., 2007), appeared in Odessa, a major seaport and transportation hub in Southern Ukraine, in 1994-1995 (Novitsky et al., 1998). Research suggests that A_{FSU} originated in the Democratic Republic of the Congo and dates the most recent common ancestor (tMRCA) of A_{FSU} in Odessa in 1984 (Díez-Fuertes et al., 2015). The tMRCA of the sub-cluster of A_{FSU} that caused the PWID-related epidemic was probably also present in Odessa in 1993, a few years before the huge explosion of HIV in PWID (Díez-Fuertes et al., 2015). A_{FSU} spread rapidly to Ukraine (Bobkova, 2013; Saad et al., 2006b), Russia (Bobkov et al., 2001, 2004a), Belarus (Lazouskaya et al., 2005; Lukashov et al., 1998), Kazakhstan (Bobkov et al., 2004b; Eyzaguirre et al., 2007), Uzbekistan (Kurbanov et al., 2003), Georgia (Zarandia et al., 2006), Latvia (Balode et al., 2012, 2004; Ferdats et al., 1999), Lithuania (Caplinskas et al., 2013), Azerbaijan (Saad et al., 2006a), Tajikistan (Beyrer et al., 2009), Armenia (Laga et al., 2015b), Kyrgyzstan (Laga et al., 2015a), and the FSU republic of Moldova (Pandrea et al., 2001). Migratory waves between the FSU states and other countries, and increasing rates of

heterosexually-acquired HIV infection have produced some changes in the molecular epidemiological patterns of FSU countries. However, A_{FSU} remains the predominant strain among drug injectors and heterosexually-infected individuals in the above-mentioned countries, including the Russian Far East, with prevalence estimates ranging between 50%-94% (Balode et al., 2012; Bobkova, 2013; Eyzaguirre et al., 2007; Kazennova et al., 2014; Lazouskaya et al., 2005; Rumyantseva et al., 2009; Saad et al., 2006a; Smolskaya et al., 2006; Zarandia et al., 2006).

Among PWID in Estonia, A_{FSU} follows in frequency the predominant CRF06_cpx strains (Adojaan et al., 2005; Avi et al., 2011; Zetterberg et al., 2004). CRF06_cpx has been identified in Africa and meets the complex designation (cpx) because 4 subtypes (A, G, K, J) contribute to genome structure (Montavon et al., 2002). Although CRF06_cpx is constricted to Estonia, it has reportedly increasingly been circulating in Saint Petersburg, the second largest Russian city (Bobkova, 2013). Recombination of A_{FSU} and CRF06_cpx has been observed in Estonia (Adojaan et al., 2005; Avi et al., 2011). CRF02_AG, a common strain in Africa, is the prevailing clade among PWID in Kyrgyzstan followed by A_{FSU} (Laga et al., 2015a). CRF63_02A1, which is a recombination of A_{FSU} and CRF02_AG (Baryshev et al., 2014, 2012), has also been detected in Kyrgyzstan (Laga et al., 2015a). CRF02_AG and its recombinants with A_{FSU} have generally become prevalent in Central Asia (Uzbekistan, Kyrgyzstan, Kazakhstan) (Bobkova, 2013; Carr et al., 2005; Eyzaguirre et al., 2007; Laga et al., 2015a; Lapovok et al., 2014) and also in Asian parts of Russia as drug trafficking routes seem to be changing (Baryshev et al., 2012). It should be mentioned that A1 has been spreading in some Central and Western European countries through sexual or injecting networks (Lai et al., 2016; Parczewski et al., 2016).

B_{FSU} (IDU-B) is a common variant in the region (Bobkova, 2013) but failed to spread widely outside of Ukraine creating mainly localized epidemics in Nikolayev, an important transportation junction of Ukraine where the strain was first identified (Nabatov et al., 2002), and in a couple of Ukrainian urban settings, including the capital city of Kiev (Bobkova, 2013; Saad et al., 2006b). B_{FSU} (IDU-B) was rare in Russia but recent analyses showed that has approximately infected 62% of PWID in Vladivostok, the largest sea port of Russian Far East (Kazennova et al., 2014). The increased prevalence of B_{FSU} (IDU-B) in the Far Eastern region of Russia is attributed to labor migrants from Ukraine (Bobkova, 2013; Kazennova et al., 2014). B_{FSU} (IDU-B) strains belong to a monophyletic clade and are distinct from subtype B sequences circulating in Western Europe. The origin of B_{FSU} (IDU-B) remains unknown (Bobkova, 2013).

A_{FSU} and B_{FSU} (IDU-B) were the parental strains of CRF03_AB, a recombinant that infected more than 2,000 PWID in Kaliningrad (Russian exclave between Poland and Lithuania) in mid- to late 1990s (Bobkova, 2013; Liitsola et al., 2000a, 1998). CRF03_AB has occasionally been detected in other Russian areas including Saint Petersburg (Lukashov et al., 1999), has produced an outbreak in Cherepovets (Northern Russia) (Bobkova, 2013; Kazennova et al., 2014; Smolskaya et al., 2006), is very prevalent in Ekaterinburg (Central Russia) comprising 23% of infections (Bobkova, 2013), and has become of epidemiological relevance in Belarus (Eremin et al., 2011) and Lithuania (Caplinskas et al., 2013).

5. Molecular Epidemiology of HIV among PWID in Western and Central Europe

Subtype B travelled from the US to Europe infecting initially MSM, and then PWID and other key populations (Glauser and Francioli, 1984; Kuiken et al., 2000; Thomson and Najera, 2007). PWID in Europe became infected either from local epidemics among MSM (Casado et al., 2000; Kuiken et al., 2000; Thomson and Najera, 2007) or from a variant circulating among PWID in North America (Lukashov et al., 1996; Thomson and Najera, 2007).

Between 70% and 85% of newly diagnosed infections in Western and Central Europe have been caused by subtype B while subtypes A, C and G circulate in less than 20% of infected persons (Abecasis et al., 2013; Bannister et al., 2006; Hemelaar et al., 2011). The prevalence of non-B subtypes has increased over the years, which has been attributed to migration from Sub-Saharan Africa and South America (Holguín et al., 2008; Paraskevis et al., 2007). Among PWID, subtype B is predominant (around 70%) followed by subtype G (10%), subtype A1 (around 5%), and CRF02_AG (3%) (Abecasis et al., 2013; Stanojevic et al., 2012). Circulating subtypes and CRFs among PWID in the region are shown in Figure 1.

Spain and Portugal experienced an enormous HIV spread among PWID in the 1990s and their epidemics are characterized by substantial viral diversity and distinct molecular properties compared to other European countries (Carvalho et al., 2015). Non-B subtypes were present among HIV+ PWID in the early years of the epidemic in Spain (Lospitao et al., 2005). Non-B subtypes, and especially subtype G (21-24%), were also very prevalent among PWID in Portugal in the late 1990s (Esteves et al., 2003, 2002), while subtype G is still found in around 30% of all diagnoses (Carvalho et al., 2015; Palma et al., 2007). Subtype G and other non-B subtypes were introduced in Portugal following intense migration between Portugal and its former African colonies in the late 1970s and early 1980s, especially because of the Portuguese Colonial War that involved multiple theatres of operation including Angola with a high degree of HIV-1 group M genetic diversity (Bártolo et al., 2009; Carvalho et al., 2015; Vermund and Leigh-Brown, 2012). Subtype G, which also circulates among PWID in Spain (Delgado et al., 2002; Pérez-Alvarez et al., 2003), recombined with subtype B, probably in Portugal early in the history of the epidemic, creating CRF14_BG that has been detected in Portugal, at low prevalence in the region of Galicia, Spain, and in some other European settings (Bártolo et al., 2011; Carvalho et al., 2015; Duque et al., 2003; Harris et al., 2005; Thomson et al., 2001). Although CRF14_BG soon became the predominant CRF in Portugal and Spain, its prevalence has been decreasing, a finding that might be associated with its high pathogenicity or its tendency to recombine with other strains, but also to the declining prevalence of HIV-1 among PWID (Bártolo et al., 2011; Carvalho et al., 2015).

Despite decreasing trends in HIV-1 diagnoses among PWID in Western Europe after 2000, Greece and Romania, and in particular their capital cities, Athens and Bucharest respectively, experienced recent PWID-related outbreaks (Nikolopoulos et al., 2015a; Paraskevis et al., 2015). The HIV-1 epidemic in Greece was concentrated in MSM (Nikolopoulos et al., 2008) being the product of multiple introductions of subtype B from

other Western countries although the prevalence of subtype A has been increasing over time (Paraskevis et al., 2007). Before 2011, HIV-1 infections among drug injectors in Greece were rather sporadic and not phylogenetically clustered indicating limited networks of transmission in this group (Paraskevis et al., 2013). In parallel with a serious economic crisis, HIV-1 diagnoses among PWID exploded in 2011 and peaked in 2012 (Nikolopoulos et al., 2015b; Paraskevis et al., 2011). The majority of the Greek PWID-related sequences fell within four transmission clusters: CRF14_BG (49%), CRF35_AD (18%), subtype B (12%), and subtype A (6%) (Paraskevis et al., 2015, 2013). The two recombinants had not been identified in samples collected before 2011 and phylodynamic analyses estimated the start of their transmission clusters in 2010-2011 (Paraskevis et al., 2015, 2013). CRF14_BG originated in strains circulating in Romania, while CRF35_AD had its origin in Afghanistan/Iraq (Paraskevis et al., 2015, 2013). Outbreak subtypes A and B originated in Greece; the B cluster begun earlier than the others, probably in 2008 (Paraskevis et al., 2015). HIV transmission among PWID in Greece seems to be subsiding as the number of diagnoses decreased in 2014/2015 (Nikolopoulos et al., 2015b) and effective reproductive numbers estimated by molecular analyses for two of the outbreak clusters had fallen below one by November 2013 (Paraskevis et al., 2015).

Subtype B prevails in HIV infections in central European counties including Poland, Slovakia, the Czech Republic, Hungary, and most Balkan states although some non-B strains including A1 have been identified, especially among persons infected heterosexually or through injecting drug use (Chabadová et al., 2014; Habekova et al., 2010; Linka et al., 2008; Mezei et al., 2011; Reinis et al., 2001; Smoleń-Dzirba et al., 2012; Stanojevic et al., 2012). In Romania, however, HIV spread probably through contaminated needles/syringes used for therapeutic injections and seriously affected newborns and children in orphanages (Hersh et al., 1993, 1991). The Romanian epidemic has been dominated by subtype F1, being a unique case in Europe (Stanojevic et al., 2012). Following decreased support from international funders and heightened injecting rates of stimulants, an HIV-1 outbreak occurred among PWID in Bucharest between 2011 and 2013 with transmission networks including one cluster based on CRF14_BG (23%) and two clusters based on F1 (20% and 50% respectively) (Niculescu et al., 2015; Paraskevis et al., 2015). F1 strains in Romania originated, in contrast to Greece, from locally circulating clades, while CRF14_BG was probably introduced to Romania from Spain/Portugal (Paraskevis et al., 2015). It is estimated that one F1 cluster started earlier (2008) than the others (2010) (Paraskevis et al., 2015).

European countries other than those described before have also experienced HIV outbreaks among PWID in the past. Contrary to the Greek and Romanian cases, previous outbreaks in Western and Central European settings were primarily caused by a single circulating clade although other strains could co-circulate as well (Paraskevis et al., 2015). For example, in the late 1990s-early 2000s in Finland, HIV affected a marginalized population of PWID with high rates of imprisonment and homelessness (Kivelä et al., 2007) and CRF01_AE, a prevalent variant in Southeast Asia that was circulating in Finland in the early 1990s, was the cause of the outbreak (Kivelä et al., 2005; Liitsola et al., 2000b; Skar et al., 2011). CRF01_AE was imported from Helsinki, Finland to Stockholm, Sweden leading there to an outbreak among PWID that started probably in around 2003 and was detected in 2006 (Skar

et al., 2011). Similarly, in a PWID-related outbreak in early 2000s in Northern Italy, HIV-1 diagnoses among PWID formed a monophyletic cluster of subtype G with origin in West Africa (Ciccozzi et al., 2007). Finally, CRF11_cpx, of African origin, has been identified in half of PWID with HIV-1 in the western part of Switzerland while B/CRF11 co-infection in that group of PWID was also frequent (5%) (Thomson and Najera, 2007; Yerly et al., 2004).

6. Molecular Epidemiology of HIV among PWID in Asia

Injecting drug use has been fueling the HIV epidemic in many parts of this region, which includes the two primary opium-producing areas in the world: the Golden Crescent defined by peripheries of mountains in Afghanistan, Iran and Pakistan, and the Golden Triangle than spans Myanmar (Burma), Laos, Vietnam, and Thailand. The major HIV strains that circulate in South and Southeast Asia are subtypes B and C, and CRF01_AE (Lau et al., 2007). Genetic complexity, however, has increased over time as multiple recombination events took place (Figure 2).

6.1. Counties of South and Southeast Asia with recombination hotspots

In Thailand, during the early years of the epidemic, subtype B (Western type B and Thai B or B') was the most prevalent clade among PWID while CRF01_AE was frequent in people infected heterosexually (Deng et al., 2008; Kijak et al., 2013; Ou et al., 1993). The ancestor of Thai B or B' existed around 1985 having diverged from subtype B and became the founder strain in South and Southeast Asia (Deng et al., 2008; Junqueira and Almeida, 2016; Li et al., 2010b). In the mid-1990s and early 2000s, however, CRF01_AE took over in PWID in Thailand (Kijak et al., 2013; Subbarao et al., 1998; Vongsheree et al., 2002) and spread among injecting drug users in other countries of the region including Cambodia, Vietnam, Malaysia, China, Taiwan, Korea, and Japan (Chow et al., 2014; Kato et al., 2001; Lau et al., 2007; Liao et al., 2009; Menu et al., 1996; Shiino et al., 2014). As a matter of fact, Thailand was the source of the CRF01_AE epidemic in the rest of Asia and Europe (Angelis et al., 2015). Some PWID in Thailand were dually infected by CRF01_AE and B (Ramos et al., 2002), and recombinants such as CRF15_01B, and CRF34_01B appeared in Thai injectors (Kijak et al., 2013; Tovanabutra et al., 2007, 2004, 2003, 2001).

Malaysia is home of a PWID-related epidemic with 70% of HIV diagnoses attributed to injecting drug use (Chow et al., 2013). Similarly to Thailand, Malaysia has been experiencing molecular shifts over the years. CRF01_AE and subtype B had been circulating among PWID (Beyrer et al., 1998; Brown et al., 1996; Saraswathy et al., 2000) but, in the early 2000s, CRF01_AE/B recombinants were detected at increasing rates (Tee et al., 2005a, 2005b). Recently, recombinants that originated in Malaysia, CRF33_01B (Tee et al., 2006), and its descendants CRF48_01B (Li et al., 2010a), CRF54_01B (Ng et al., 2012), and CRF58_01B (Chow et al., 2014) have been identified in PWID. A recent study based on samples collected between 2010 and 2011, found that the prevalence of CRF33_01B among PWID in Kuala Lumpur was very high (71%) followed by subtype B' (11%), CRF01_AE (5%), and CRF01_AE/B' unique recombinants (13%) (Chow et al., 2013). CRF33_01B has also been detected in other countries of the region (Sahbandar et al., 2009).

Major strains circulating in China include subtype B' (9.6%), CRF01_AE (27.6%), CRF07_BC (35.5%), and CRF08_BC (20.1%) (Han et al., 2015; He et al., 2012; Laeyendecker et al., 2005). Subtype C is currently a minor clade with a prevalence at 1.6% (He et al., 2012). Injecting drug use may still account for around half of HIV transmissions in China (He et al., 2012). Among PWID, the most updated studies showed that the subtype distribution is: CRF01_AE (21.2%), CRF07_BC (48.5%) and CRF08_BC (23.6%) (He et al., 2012). The province of Yunnan that is located in the Southwest part of China and shares borders with Vietnam, Laos, and Burma (Myanmar), has played an important role in HIV spread in China and serves as a hotspot of genetic mixing due to its closeness to the Golden Triangle and the heroin trafficking routes (Beyrer et al., 2000). Subtype C from India and subtype B from Thailand caused the first outbreaks among PWID in Yunnan in the late 1980s and early 1990s (Han et al., 2015; Piyasirisilp et al., 2000; Tee et al., 2008; Zheng et al., 1994). Subtype B', that soon became the predominant B clade in China (Graf et al., 1998; Lau et al., 2007), and subtype C recombined to generate two related but distinct strains, CRF07_BC and CRF08_BC, which trace their origin to Yunnan and fueled the epidemic among PWID in Northwestern, Southeastern and Northeastern China, and to Taiwan (CRF07_BC) (Han et al., 2015; He et al., 2012; Laeyendecker et al., 2005; Lau et al., 2007; Li et al., 2015; Lin et al., 2006; Piyasirisilp et al., 2000; Takebe et al., 2010; Tee et al., 2008). CRF07_BC has also become the predominant strain among PWID (>80%) in Taiwan (Chen et al., 2012, 2010; Huang et al., 2014; Lin et al., 2006). Finally, CRF01_AE, imported from surrounding countries and following drug trafficking routes, was detected in PWID in the provinces of Yunnan, Guangdong, and Guangxi in the mid-1990s (Beyrer et al., 2000; He et al., 2012; Yu et al., 1999). CRF01_AE strains, related to those circulating in Guangxi and other Chinese prefectures, have been identified in transmission clusters containing PWID in Hong Kong (Chen et al., 2009). Molecular analyses have showed that the CRF01_AE epidemics in China and Vietnam were monophyletic suggesting regional dispersal (Angelis et al., 2015).

PWID in Myanmar (Burma) have been infected by subtype B, CRF01_AE, and various recombinants. Subtype B is predominant among PWID in Southern Myanmar but the proportion of CRF01_AE and recombinants is elevated in central regions (Kusagawa et al., 1998; Motomura et al., 2000; Takebe et al., 2003; Zhou et al., 2014). However, the northern part of Myanmar, which shares borders with the Chinese province of Yunnan, is very interesting in epidemiological terms as the majority (>85%) of PWID in the region carry recombinant strains (Liu et al., 2012; Pang et al., 2012; Zhou et al., 2014). Travel, trade and intermarriage across the Myanmar-China borders are common. Dehong prefecture of Yunnan province that includes Ruili district, where the first PWID outbreak in China was detected, has been an important hub of drug trafficking from the Golden Triangle into China and large numbers of PWID, both Burmese and Chinese, cross the Myanmar-China borders to inject drugs (Han et al., 2013; Zhou et al., 2014). Both sides of the borders region have high prevalence of recombinants (>80%) (Han et al., 2013; Pang et al., 2012; Zhou et al., 2014). The proportion of CRF01_AE-related recombinants (CRF01_AE/B'/C or CRF01_AE/C) is higher in Northern Myanmar than in Dehong, China where B'/C recombinants prevail (Han et al., 2013; Pang et al., 2012). This finding suggests that events of genetic mixture in Dehong and Northern Myanmar are, to some degree, independent.

Beyond drug injectors who cross the borders and become infected probably by multiple co-circulating strains, other factors may contribute to high levels of genetic heterogeneity in the region. For instance, Burmese long-distance truck drivers who drive between Mandalay, Myanmar and Ruili, China, are engaged in unprotected sex with occasional, multiple partners or sex workers, and some of them also inject drugs (Zhou et al., 2014). These drivers may serve as a bridge of bidirectional transmission between heterosexuals and PWID on both sides of the borders (Zhou et al., 2014).

6.2. Other countries in South and Southeast Asia

CRF01_AE predominates in Cambodia, which has experienced high transmission rates among heterosexuals and HIV prevalence was more than 20% in PWID (Kusagawa et al., 1999; Lau et al., 2007; Menu et al., 1999; Strathdee and Stockman, 2010). In Indonesia, analyses have shown a high prevalence (>90%) of CRF01_AE among drug injectors (Lau et al., 2007; Sahbandar et al., 2009). However, recombinants, including CRF33_01B, have been found (Sahbandar et al., 2009). CRF01_AE, introduced from Thailand to heterosexuals and drug injectors in South Vietnam, is also the major clade circulating among PWID in the country (Lan et al., 2003; Liao et al., 2009). Cross-border transmissions between Northern Vietnam and the Guangxi province of China have been reported (Kato et al., 2001, 1999; Liao et al., 2009). In Japan, drug injectors significantly contributed to CRF01_AE spread, which is the second most prevalent clade after subtype B (Shiino et al., 2014).

6.3. India, Nepal, Bangladesh

India hosts more than 2.5 million people with HIV (Neogi et al., 2012; Shen et al., 2011) and the prevalence in PWID in some settings is as high as 30% with half of the infected being unware of their infection (Armstrong et al., 2015; Goswami et al., 2014). Subtype C is the major strain circulating among HIV-infected people in India and Nepal including drug injectors (Lau et al., 2007; Mandal et al., 2002; Neogi et al., 2012, 2011; Oelrichs et al., 2000; Shahid et al., 2011; Shen et al., 2011). Recombinants of subtypes B and C, and CRF01_AE have been identified in these countries (Bhanja et al., 2005; Mullick et al., 2010; Sarkar et al., 2009; Shahid et al., 2011; Tripathy et al., 2005). HIV prevalence is generally low in the neighboring country of Bangladesh but is more than 5% in PWID in Dhaka, the capital of Bangladesh (Bontell et al., 2013). The epidemic in general and among PWID is subtype C-driven, and strains cluster with viruses from India and Myanmar (Azim et al., 2002; Bontell et al., 2013; Sarker et al., 2008).

6.4. Afghanistan, Iran, Pakistan (Golden Crescent)

Drug injection is the main route of HIV transmission in Iran (~70% of diagnoses) with a prevalence in PWID around 15% (Baesi et al., 2014; Khajehkazemi et al., 2013; Memarnejadian et al., 2015). CRF35_AD is the predominant strain in Iranian drug injectors and clusters with CRF35_AD infections detected in Afghanistan (Baesi et al., 2014; Jahanbakhsh et al., 2013a, 2013b; Memarnejadian et al., 2015; Mousavi et al., 2010). CRF01_AE has rarely been detected in samples of drugs injectors in Iran (Jahanbakhsh et al., 2013b) and subtype A had been identified in the past (Naderi et al., 2006; Sarrami-Forooshani et al., 2006; Tagliamonte et al., 2007).

Afghanistan is the primary producer of opium worldwide but HIV prevalence was relatively low in mid-2000s at around 2-3% (Sanders-Buell et al., 2010, 2007). However, in that period, a novel recombinant, CRF35_AD, was first identified in PWID in Afghanistan and is the major strain in that group (Sanders-Buell et al., 2010, 2007). The genetic relatedness of CRF35_AD strains circulating in Iran and Afghanistan suggests transmission linkages between PWID of these countries due to migration or through drug trafficking as Iran lies on the drug trafficking pathway between Afghanistan and Europe (Baesi et al., 2014).

The HIV epidemic has been growing in Pakistan affecting also the population of injecting drug users with increasing trends in HIV prevalence from around 15% in 2006 to around 30% in 2011 (Altaf et al., 2009; Archibald et al., 2013; Shah et al., 2011). Although CRF35_AD has been found in HIV positives in Pakistan, subtype A1 is the most frequent clade among PWID (Khan et al., 2006; Shah et al., 2011).

7. Conclusion

Injecting drug use is a risky practice associated with increased likelihood of HIV acquisition. Over the last 30 years, millions of PWID became infected with an estimated overall mortality almost 3 times higher among HIV positive than among HIV negative drug injectors (Mathers et al., 2013). In addition, PWID serve as bridges of HIV transmission into other groups including the general population. For instance, nowadays in New York, a city that suffered a huge epidemic among PWID in the 1980s and 1990s but succeeded in containing it in 2000s, especially by increasing access to sterile injecting equipment and ART, HIV prevalence is higher in non-injecting drug users than in PWID (Des Jarlais et al., 2011). High rates of heterosexual transmission of HIV have been observed in FSU countries following the mega-epidemics among PWID during the 1990s (Bobkova, 2013; European Centre for Disease Prevention and Control (ECDC)/World Health Organization (WHO), 2014). However, on the other hand, comprehensive prevention approaches have been developed including scaling-up HIV testing, distribution of clean injection equipment, and increased access to substitution programs and ART that can significantly reduce infection rates in PWID (Abdul-Quader et al., 2013; Aspinall et al., 2014; Des Jarlais et al., 2013; MacArthur et al., 2014).

Molecular epidemiology has revealed underlying patterns of HIV spread that traditional epidemiological methods are inherently unable to capture. For example, we know that starting in Odessa, Ukraine, a major seaport of the Black sea, a particular variant, subtype A1, spread at impressively rapid rates among PWID and to almost every part of the former Soviet Union. Contrary to patterns seen before in Western/Central Europe, Greece and Romania experienced PWID-related outbreaks consisted of multiple transmission clusters. One of the clusters (CRF35_AD) in Greece had its origin in circulating strains in Afghanistan/Iran. This finding indicated the role of population movement in HIV spread, which should be taken into account when public health interventions are designed and implemented. As a matter of fact, in Greece, successful efforts to contain the epidemic (Hatzakis et al., 2015) targeted migrant groups. Finally, the borders of China, Myanmar, Laos, and Thailand comprise a big spot of genetic exchanges between HIV variants circulating in PWID and other key populations of different ethnicities producing novel

intersubtype and inter-CRF recombinants. This is a major issue of public health concern as novel strains may further complicate the process of vaccine development, increase transmission and disease progression rates or change patterns of resistance to antiretrovirals (Abecasis et al., 2006; Baeten et al., 2007; Brenner et al., 2003; Renjifo et al., 2004; Stephenson and Barouch, 2013). In addition, molecular epidemiology has shown that HIV spreads in many parts of this region following routes of illicit drugs trafficking, which clearly shows that it might be hard to control HIV unless appropriate measures are taken to limit drug markets and trafficking.

Taken all findings together, it seems that routine systems of collecting, analyzing and interpreting molecular information are urgently needed if we do want to understand better and deeper HIV diversity and its public health implications.

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Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ART	antiretroviral treatment
CDC	United States (US) Centers for Disease Control and Prevention
CRFs	circulating recombinant forms
FSU	Former Soviet Union
HIV	Human Immunodeficiency Virus
MSM	men who have sex with men
PrEP	pre-exposure prophylaxis
PWID	people who inject drugs
SIV	Simian Immunodeficiency Virus
TaSP	treatment as prevention
tMRCA	time of the most recent common ancestor
UNAIDS	United Nations Joint Programme on HIV/AIDS (UNAIDS)
URFs	unique recombinant forms
WHO	World Health Organization

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Highlights

- Molecular studies reveal patterns of HIV spread among People who Inject Drugs (PWID).
- A_{FSU}, B_{FSU} (IDU-B), and CRF03_AB produced big epidemics in Former Soviet Union states.
- Subtype G and CRF14_BG caused big epidemics in Portugal/Spain.
- Transmission clusters (B, A, F1, CRF14_BG, CRF35_AD) were observed in Greece/Romania.
- CRF35_AD is the most prevalent clade among PWID in Afghanistan/Iran.
- Recombination hotspots in South-East Asia have been generating several recombinants.

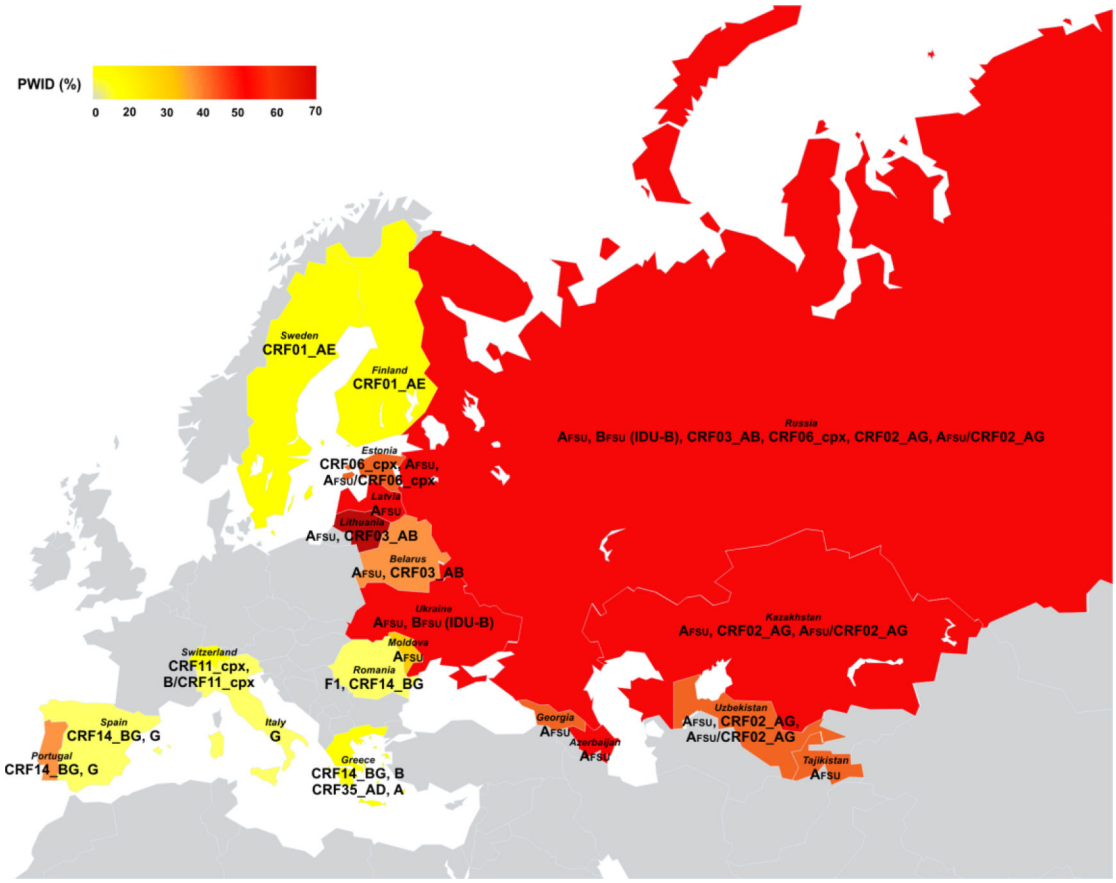

Figure 1.

Distribution of HIV-1 variants among people who inject drugs (PWID) in Europe and Central Asia.

Abbreviations: CRF, circulating recombinant form; FSU, Former Soviet Union; PWID: people who inject drugs.

Note: Colors reflect the proportion of PWID among newly diagnosed cases of HIV infection. The color for Russia is based on 2013 data retrieved from the UNODC (United Nations Office on Drugs and Crime (UNODC), 2014). For the rest of the countries, colors are based on 2014 data retrieved from the ECDC/WHO (European Centre for Disease Prevention and Control (ECDC)/World Health Organization (WHO), 2014). In the gray region, subtype B predominates.

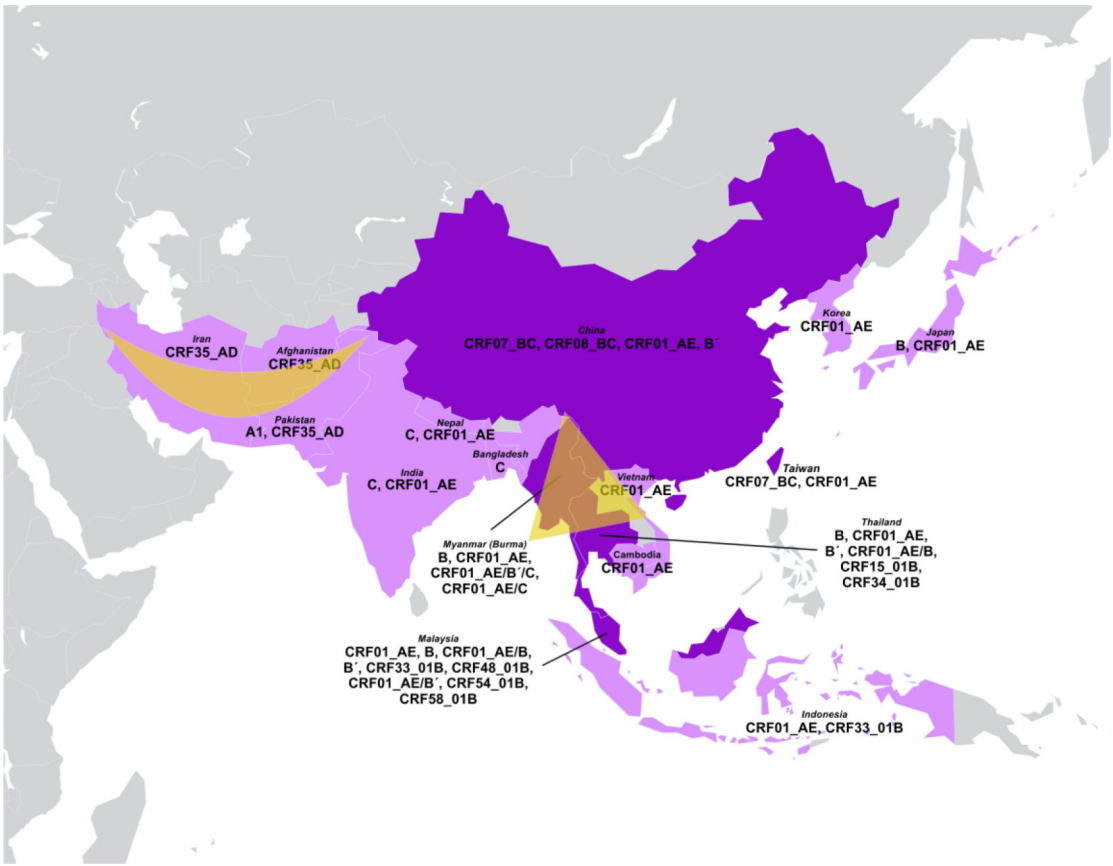

Figure 2.

Distribution of HIV-1 variants among people who inject drugs (PWID) in Asia.

Note: Deep purple highlights countries that include hotspots of genetic recombination between HIV-1 strains. Major areas of opium production include the Golden Crescent defined by peripheries of mountains in Afghanistan, Iran, and Pakistan and the Golden Triangle that spans Myanmar (Burma), Laos, Vietnam, and Thailand.