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State of the Art in HIV Drug Resistance: Surveillance and Regional Gaps

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Abstract

This article is the second of a two-part review aiming to identify gaps in the knowledge and management of human immunodeficiency virus type 1 drug resistance (HIVDR) from global and regional perspectives. Here, we examine the policy and programmatic gaps in HIVDR surveillance, the affected populations and settings, and implications for clinical practice. The expert authorship of this review convened to identify gaps in HIVDR surveillance, with a particular focus on specific regional variations within and between Europe and Asia, to highlight directions for research and implementation. Further, evidence was gathered from a review of published studies, guidelines, and current practices. This review found that despite recent progress in the development, harmonization, and implementation of guidelines on HIVDR reporting and surveillance, programmatic, and policy gaps reflect the regional variability in HIV epidemics, clinical practice, and resources. The need for representative surveillance was identified as a key gap that has the potential to inform management policies. Monitoring must keep up with the evolution of transmission routes to adapt appropriately, and this will be further impacted by migration from areas with increasing levels of resistance. Analysis of the latest clinical data, regional practice, policy, and guidelines has identified a number of gaps in HIVDR population monitoring and surveillance. More efforts are needed to align surveillance platforms with harm reduction and patient education, particularly in vulnerable subgroups. Addressing these gaps will facilitate research into and progress in the management of HIV across a wide range of health-care settings. (AIDS Rev. 2018;20:42-56)

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Introduction

Over the past decades, human immunodeficiency virus (HIV) treatment options have become more effective in delaying the evolution of drug resistance and improving the outcomes of antiretroviral therapy (ART). However, for some patients, especially those from low-resource regions or care settings, HIV-1 drug resistance (HIVDR) still poses a serious threat to health[1-4].

Recent progress notwithstanding, there is an ongoing need for improved, concerted, and systematic efforts directed at HIVDR surveillance in both high- and low-income countries, and, more broadly, a need for policies and programs, guidelines, and training to support the regional management and prevention of HIVDR in a wide range of patient populations and health-care settings.

In a companion review, we examined gaps in the knowledge and understanding of acquired HIVDR mutations (ADRM) to identify priorities for research and scientific exchange in the clinical management of HIV disease[5]. The objective of this review is to discuss key gaps in population monitoring and surveillance of HIVDR with a focus on regional variations in practice to further the understanding, control, and prevention of drug resistance.

Monitoring and surveillance

Recent data on the prevalence of HIVDR have highlighted the need for increased monitoring and surveillance. Despite the decrease in ADRM in patients experiencing treatment failure, the prevalence of transmitted drug-resistance mutations (TDRMs) is stable in Europe - currently at ~10%[1,6-8]. In contrast, the prevalence of TDRM is lower in areas where ART has been more recently introduced, but it is increasing over time[4,7,9].

In the START study, resistance testing from 1946 participants identified a global TDRM prevalence of 10.1%[10]. Thymidine analog mutations (TAMs) such as M41L and T215F/Y, as well as the T215D/C/E/S/N revertants, are commonly identified, reflecting the persistence of these mutations in the population despite the declining use of zidovudine (AZT) and stavudine[8,10-14]. Other mutations become less prevalent following transmission, for example, M184V/I, and these may go undetected by standard sequencing, yet still exert clinical significance[15-17]. Furthermore, pretreatment levels of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance now exceed 10% in many countries. Although pretreatment NRTI resistance is lower than that of NNRTI resistance, it was recently reported by the World Health Organization (WHO) to be increasing in Eastern and Southern Africa[4]. Addressing the challenges, this poses is implicit for achieving the WHO target of 90% virologic control for all patients on therapy[4]. As NNRTIs are an essential component of currently recommended first-line ART, the WHO guidelines on the public health response to pretreatment HIV drug resistance include new recommendations to consider changing a country's first-line ART regimen if levels of pretreatment NNRTI drug resistance reach 10%. This is an important step forward in the global response to HIVDR[4].

Routine viral load (VL) monitoring and viral genotyping help clinicians tailor treatment choices to patients' needs while reducing the risk of drug resistance and unnecessary treatment switches[18]. Current clinical guidelines highlight that, as an indicator of clinical response, routine VL monitoring allows for early identification of virological failure and reduces the potential for resistance development[19,20]. The value of VL monitoring is well defined and has been reinforced by a meta-analysis of 8376 patients from 10 cohorts/studies, in which NNRTI resistance at treatment failure in patients infrequently monitored was significantly higher than in those undergoing frequent monitoring (88.3% vs. 61.0%)[21].

Surveillance of ADRM and TDRM data provides epidemiological information regarding HIV infection and transmission and helps inform public health policies[4,21]. Population surveillance is crucial for providing data on early warning indicators of resistance, particularly in regions where ART switching is often based on clinical criteria alone[2,4]. The WHO HIVDR network (HIVResNet laboratory working group) was established to develop and support HIVDR prevention, surveillance, and mon-

itoring during the global scale-up of ART and provides valuable information[4].

Despite advances in the field, several programmatic and policy gaps exist in the monitoring and surveillance of HIVDR (Table 1).

Table 1. Gaps in the monitoring and surveillance of HIVDR

Gaps: Resistance monitoring
General surveillance
1. Renewed need for representative surveillance
2. Surveillance of patients failing therapy or at high risk of failure, including funding issues
3. Updates and interpretation of the surveillance drug-resistance mutation list
4. Lack of local and cluster analyses in specific settings
Standardization and coordination
5. Need for coordinated and standardized reference framework within a global system of quality control
Cluster surveillance
6. Need for an updated review of mutations preferentially found and transmitted in clusters

HIVDR: human immunodeficiency virus type 1 drug resistance.

General surveillance

Gap 1: Renewed need for representative surveillance

Surveillance studies are often conducted using specific methodologies that are not consistent between populations or in terms of the types of sampling and laboratory methods employed. Furthermore, regional factors may also lead to disparity between studies. As such, surveillance data may not always provide a true representation of the patient population or, therefore, reliable estimates of the regional prevalence of drug resistance[4]. This represents a significant gap in how surveillance practices are conducted. Consistent and systematic sampling of patients before ART initiation can provide reliable and representative data with continuity between centers[3], but there are additional considerations with regard to timing and interpretation.

Early after infection, during the period when major resistance mutations tend to reverse, the benefit of sensitive testing for TDRM detection increases with the duration of infection and with the increase in sensitivity to detect minority variants. As infection progresses, such minority-resistant variants may no longer be detected, even with sensitive testing. These are factors to be considered when evaluating the time window and detection limit cutoff for such sensitive testing. This is particularly true for NNRTIs with a low genetic barrier to resistance, which can lead to multiple independent NNRTI-resistant viral subpopulations[15,17]. Knowledge of the presence of baseline mutations, before treatment initiation in the case of TDRM and at treatment failure for ADRM, can improve clinical decision-making, thereby decreasing the likelihood of subsequent treatment failure.

Four NNRTI-resistance mutations (K101E, K103N, Y181C, and G190A) represent the majority of high-level TDRM across all regions and viral subtypes; and 16 NRTI-resistance mutations account for more than 69% of NRTI-related TDRM across all regions and subtypes[7,8]. Such surveillance data support the need for baseline resistance testing, particularly in areas with high TDRM levels. It remains to be determined whether transmission efficiency of TDRM is correlated with VL, but transmission of viruses with resistance mutations accompanied by compensatory mutations may explain the persistence of some mutations (e.g. M41L) and supports the need for further baseline resistance testing[16].

Further, to optimizing representative surveillance practice, understanding the impact of single transmitted mutations is also important. Likewise, there needs to be consideration of whether such mutations are part of single mutation transmission cluster - transmitted from an ART-naive patient - or whether additional, hidden resistant variants are present, resulting from transmission from a patient failing treatment. For example, NRTI-related M41L in reverse transcriptase can confer resistance to NRTIs in the presence of other TAMs - albeit to a variable extent - but, as a single TAM, may decrease replicative ability[22]. Studies suggest that minority variants conferring resistance are rare in patients with a single transmitted NRTI mutation, and a single M41L mutation at baseline may not influence the development of resistance to tenofovir-containing regimens[23,24]. These findings require larger studies to confirm their meaning and determine their impact on clinical practice.

Gap 2: Surveillance of patients failing therapy or at high risk of failure, including funding issues

Representative sampling with continuity between centers will require large numbers of patients for an accurate analysis of failure risk. The acquisition of such data will require policy, and thereby economic-level changes, balancing poor funding for transmission sur-

veillance with longer-term financial implications of resistance[3].

In high-resource settings, large-scale population surveillance programs are feasible and provide insight into the broad determinants of virological failure risk, thus informing ART selection in the first and subsequent lines of treatment[25]. For example, an analysis of the effect of TDRM on treatment outcome in the 1st year of combination ART in 10,056 patients from 25 cohorts, including the UK HIV Drug Resistance Database, found that patients with TDRM who started a regimen containing two NRTIs plus one ritonavir-boosted protease inhibitor (PI) and received fully active treatment had a similar risk of virological failure to those showing no TDRM[26]. Current guidelines recommend the use of at least two (preferably 3) active drugs in the instance of resistance mutations, including one fully active boosted PI and one drug from a class not previously used[20].

Understanding the evolution by the calendar year of TDRM is also helpful for guiding treatment decisions, particularly treatment initiation. This has been emphasized in an analysis of TDRM patterns in 4140 patients from the European SPREAD surveillance program (strategy to control SPREAD of HIV drug resistance), followed since 2001[27]. These data have indicated that the overall prevalence of transmitted drug resistance in Europe did not change significantly during the study period and stood at 8.3% from 2008 to 2010. NRTI mutations were the most frequent TDRMs at 4.5%, with NNRTI mutations occurring at 2.9% and PI mutations at 2.0%. The prevalence of mutations associated with different drug classes did not change significantly over time[27]. However, in patients identified as recently infected, the prevalence of transmitted resistance was 10.1%, with a higher prevalence of TDRM from NRTI, NNRTI, and PI drug classes. Significantly, K103N was identified in 3.35% of recently infected patients versus 1.49% of patients with unknown infection duration[27].

In regions, where genotypic resistance testing before therapy initiation is not readily available, surveillance of TDRM is particularly important to help identify populations at high risk of treatment failure who would benefit from baseline resistance testing or for whom ART recommendations may need to be modified[3,17]. Regardless of sporadic surveillance in these regions, due to limited experience and/or resources, constant evaluation of treatment outcomes and gradual introduction of VL monitoring as part of standard practice can facilitate timely detection of treatment failure and switching to an active therapy to prevent the occurrence of TDRM and new infections. Funding such programs have proven benefits, as was demonstrated in an observational study in Mozambique, which evaluated patterns of drug-resistant mutations in adults failing the first-line ART[28]. To generate an accurate understanding of failure risk, it will be keyed to analyze large numbers of patients.

Gap 3: Updates and interpretation of the surveillance drug-resistance mutation (SDRM) list

The SDRM list was compiled by consensus agreement to distinguish between mutations originally resulting from drug selective pressure, and polymorphisms which may also affect susceptibility to drugs, to promote surveillance data and interpretations comparable between centers and regions over time[29]. The SDRM list is currently composed of 93 mutations known to cause antiretroviral (ARV) resistance. The 2013 updates to the list included raltegravir-resistant mutations L74M, T97A, E138A/K, and G140A/S[30].

Continual updating of the list as more ARVs become available and/or new mutations or cross-resistance mutations are identified[30], as well as the inclusion of polymorphic mutations and data regarding prevalence and subtypes, will enhance its scope and usage[31] and enable classification between polymorphisms and drug-selected mutations as they appear over time[7]. Less well characterized are dolutegravir-resistant mutations so that clinical interpretation tools such as HIV-DB, ANRS, REGA, geno2pheno, HIV-TRePS, and HIV-GRADE, which can be used simultaneously, still show minor differences[32-35]. Such tools are distinct from the SDRM mutation list; they are less useful for surveillance purposes and aim at predicting treatment failure. There is a tendency to refer to the SDRM list for TDRM and clinical interpretation tools for ADRM, but whether such a distinction is required remains to be determined and presents a need to update the interpretation of drug resistance for surveillance purposes.

Gap 4: Lack of local and cluster analyses in specific settings

Phylogenetic analysis is an important component of HIVDR surveillance because it helps delineate the introduction and dissemination of viral subtypes in different regional settings, identify patterns of transmission underlying subgroup epidemics, and understand the biological, demographic, and social determinants of viral cluster networks[36]. These, in turn, can help design interventions aimed at curbing HIVDR and highly localized educational campaigns targeted at distinct HIV-infected populations.

The molecular epidemiology of HIV-1 in Europe is highly stratified according to risk group[37]. At present, the fastest growing epidemics worldwide is within the injecting drug user (IDU) population in Eastern Europe (EE) and Russia, with a high prevalence of the A1 and circulating recombinant forms (CRF) CRF03_AB and CRF02_AG subtypes[38]. In heavily populated regions, including India, China, and Southeast Asia, a shift has occurred toward sexual transmission (also seen in EE), with the selective expansion of C, CRF07_BC, CRF08_BC, and CRF01_AE subtypes among the heterosexual risk group[36].

A global phylogeographic study of subtype B strains has revealed the sources and targets of virus migration and the intercountry transmission pathways[39]. Although precise geographic tracking of transmission patterns is difficult due to the complexity of the HIV epidemic, prospective monitoring of the expansion of drug-resistant subepidemics should be ongoing, and intervention strategies should include tourists, travelers, and migrants[36,39].

While subtype B continues to account for 70% of HIV-1 infections in newly diagnosed patients living in Europe[37], crossover of non-B subtype epidemics in domestic men who have sex with men (MSM), IDU, and/or heterosexual epidemics have been observed in the United Kingdom, France, Germany, Greece, Italy, The Netherlands, Canada, Belgium, and Israel, among others[12,36,37,40].

High rates of TDRM among ART-naive MSM and IDU populations have also been related to onward transmission among ART-naive patients[6,36,41-43]. Through the identification of such transmission clusters and their correlation with transmission routes and risk behavior[44], phylodemographics can be of importance in the surveillance of the rising MSM epidemics among young adults and racial/ethnic minorities[36,45].

In contrast to the MSM and IDU epidemics, heterosexual populations show infrequent clustering and low cluster size. Furthermore, there is a paucity of data on the phylodynamics of heterosexual and non-B subtype epidemics, particularly in endemic resource-limited settings[36].

Standardization and coordination of surveillance

Gap 5: Need for coordinated and standardized reference framework within a global system of quality control

Epidemiologically driven surveillance is variable. Regional, or even global, reference laboratories operating within a validated system of quality control to provide standardized outputs would be an ideal scenario in the surveillance and characterization of HIVDR. As next-generation deep-sequencing techniques become more widely available, their use with respect to minority variants requires careful protocols to define the optimal level of sensitivity for clinical significance, and potentially by drug class[5]. The role of centralized laboratories in data interpretation remains to be determined but could prove valuable in guiding clinical decisions. Bioinformatics tools such as RECall (British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada) will facilitate the development of standardized protocols and the objective analysis between clinical and research centers[46]. Some of the interpretation tools used to predict acquired phenotypes, which are based on data-driven bioinformatics systems like geno2pheno, are freely available online and still under development (www.geno2pheno.org). In turn, this benefits the community with extensive data and knowledge that has the potential to identify more resistance markers to isolate large phenotypic shifts in viral resistance.

Cluster surveillance

Gap 6: Need for an updated review of mutations preferentially found and transmitted in clusters

Large and systematic sampling is required for an accurate assessment of failure risk, but there is also a need for localized data and characterization of cluster transmission in specific settings. Cluster size varies by country and is influenced by the interconnectivity between countries. Data are, however, lacking because pooling of dense sampling between countries and risk groups needs large and consistent consortia, which are difficult to set up and maintain. There are also ethical concerns with making such data readily available. Where it has been carried out, dense sampling of epidemics has identified clusters spanning multiple countries, especially within MSM and IDU populations, highlighting the importance of such reporting[36,47,48].

For example, a phylogenetic analysis of 14,061 HIV-1 *pol* gene sequences from both treatment-naive and treatment-experienced individuals within the UK identified five clusters containing mutations that offered cross-resistance to ARVs[43]. Among the MSM risk group, drug-resistance lineages included K219Q, D67N, M41L, and T215Y (NRTI), and L90M (PI)[43]. Phylogenetic clustering of MSM infections (n = 1359) in Montréal, Canada, revealed six MSM clusters harboring K103N, V108I, or G190A; other frequently transmit-

ted species included the L90M protease mutation and TAMs (M41L, D67N, T215 revertants, and K219Q)[36].

A recent meta-analysis of 50,870 individuals from 111 countries defined a SDRM cluster as a set of three or more related viral sequences with identical SDRMs[7]. In this analysis, no clusters were identified in sub-Saharan Africa or South/Southeast Asia, and only 5% of related sequence pairs contained an identical SDRM. A single NNRTI cluster (K103N) was identified in Latin America/Caribbean, and a single PI cluster (L23I) was identified in former Soviet Union countries. North America, Europe, and higher income countries in Asia had a higher prevalence of SDRM clusters (22, 21, and 19, respectively), the most common being NNRTI K103N and G190A, NRTI T215 revertant, and PI M46I[7].

Clusters of stably transmitted resistant variants are likely to become apparent when populations undergoing surveillance are geographically concentrated and/or compartmentalized. Although such clusters may complicate SDRM updates, their possible public health significance cannot be ignored[49]. Data on transmission cluster mutations are consistent among different countries. For example, results from an MSM predominant Spanish cohort[44] confirmed the UK findings with regard to TDRM in this group[43], i.e. the 215 revertant, M41L, and 219Q/R/N/E.

The ability of TDRM to spread within a population has implications on the effectiveness of public health programs, but this has not been well characterized. Comparisons of prevalence in ART-naive versus ART-experienced patients from the same epidemic can give an idea of the propensity of particular mutants to spread in transmission clusters, and this propensity has been related to the fitness cost of the mutation[15]. A recent study assessed the transmission fitness of 69 resistance mutations using the US Centers for Disease Control and Prevention's National HIV Surveillance System network of more than 66,000 HIV-infected patients[50]. 23 mutations were found to decrease transmission fitness, and these were mostly NRTI mutations. However, other major high prevalence mutations tended to exhibit transmission fitness similar to that of wild-type virus, such as K103N and Y181C[50]. Viruses with these and other persistent resistance mutations were found to form large transmission clusters with lengthy transmission chains, sustained by enduring reservoirs in ART-naive populations. Such analyses can be pivotal in informing treatment strategies, but their impact will be greatest in countries that carry out routine resistance testing[50]. This highlights both the need for appropriate cluster surveillance and the role of testing on clinical practice.

Nevertheless, there is a scarcity of reviews detailing which mutations are typically found in big clusters, which are preferentially transmitted among clusters, and where they exist geographically. In addition, particular mutations tend to be derived mainly from transmission clusters, while others are almost exclusively transmitted from a treated patient (e.g., I84V). In this context, phylogeographic analyses detailing which mutations are circulating and what transmission routes are followed would be of particular interest.

East meets west: regional gaps

Even though TDRMs are more prevalent in high-income countries today, the overall impact on patient outcomes may be lower in those countries because genotyping at ART initiation is commonly standard practice[1,21]. In low-income regions, patients with TDRM may receive insufficiently effective ART regimens if resistance is not detected, meaning decreased effectiveness in reducing the VL, which, in turn, can lead to the evolution of multiclass drug resistance. In addition, even if testing is performed, fewer second-line treatment options are available for patients in low-income countries[1-4]. In resource-limited settings, the WHO recommends the monitoring of early warning indicators, a set of patient and clinic factors associated with the emergence of preventable HIVDR[2]. In addition, in these settings, low-cost technologies to diagnose and monitor HIV infection are crucial, and efforts have been made to develop point-of-care technologies that are affordable and robust[18,51].

The gaps in the knowledge, policy, and clinical practice of HIVDR management in EE, Asia, and Western Europe were focused on by the authors in this expert meeting, and reflect the demographic, economic, and cultural differences among these regions (Table 2).

High prevalence EE regions

Gap 1: Limitations of current regional surveillance practices

EE, particularly those countries formerly in the Soviet Union, shows demographic and molecular epidemiology trends in HIV infection that are similar to countries from Central Asia (CA). These two regions are the only areas where new HIV infections have continued to increase rapidly, with the epidemic focused on key high-risk populations. Discussion of regional-specific gaps will, therefore, concentrate on these geographies,

Table 2. Gaps in regional practice, knowledge, resources, and culture

Gaps: Regional practice
High prevalence Eastern European regions
1. Limitations of current regional surveillance practices
2. Need to better characterize and manage current transmission routes
Asia
3. Limitations of current regional surveillance practices
4. Need to characterize the shift to sexual transmission within the MSM population
Western Europe
5. Limitations of current regional surveillance practices
6. Need for improved surveillance of integrase inhibitor resistance testing in naive patients
7. Surveillance of minority groups and the shift toward non-B subtypes
8. Lack of data regarding the impact of migration

MSM: men who have sex with men.

with comparison to Western Europe where transmission rates are lower, and surveillance practices established[52]. EE and CA also show similarities in health-care infrastructure and regional practice, as well as sharing some of the gaps thereof. Differences among individual countries are far outweighed by their commonalities and, in both EE and CA, the target groups for HIV infection and the extent of HIV drug-resistance testing are significantly different from those in developed countries[53]. Two countries, the Russian Federation and Ukraine, account for more than 85% of the people living with HIV in the region[54]. The main challenges related to HIVDR in the former Soviet Union countries are related to the low ART coverage (< 40%), low treatment adherence, and drug supply interruptions[53].

A considerable number of gaps exist with regard to the understanding and monitoring of acquired and transmitted HIVDR across all patient groups in EE and CA (Table 2).

HIV genotyping has been available in Russia for several years and is becoming accessible to patients in Armenia, Belarus, Ukraine, Kazakhstan, and Uzbekistan. However, although baseline genotyping is a mandatory component of the management strategy, a lack of funding means it is not generally carried out as part of routine clinical practice[53]. While HIVDR has not been studied systematically and little data have been presented to the scientific community, cumulative research observations made in treatment-naive patients from former Soviet Union countries suggest that the prevalence of HIV drug-resistant variants in this group does not exceed 7%[53]. Among other EE and CA countries, data obtained in treatment-naive patients show a prevalence of HIVDR mutations between 1.5% in Armenia and 7.0% in Kyrgyzstan, with M184I, K65R, K219Q, Y181C, K103N, and G109S most commonly identified[55,56]. Problems with irregular drug supply and, possibly, low adherence and psychosocial well-being challenges, may lead to a rapid growth in these numbers nonetheless[57]. Such findings support the urgent need to develop a shared HIV drug-resistance monitoring system for former Soviet Union countries to better control the HIV epidemic in the region[53].

HIVDR analysis is conducted in Russia for those patients experiencing treatment failure. Among the HIVDR mutations observed in Russian patients, the most frequently reported are G190S, K101E, K103N, M184V/I, T215Y, Y181C, and M46I/L[58,59]. In other EE and CA countries, HIV genotyping method is in the implementation phase. The quality control system for HIV genotype analysis has not been developed yet, and no reference centers have been established.

Gap 2: Need to better characterize and manage current transmission routes

The distribution of HIV subtypes in EE and CA is determined by the economic and cultural relationships between the countries and has been shaped by growing migration. Molecular epidemiology data have demonstrated the preservation of a relatively low diversity of HIV-1 subtypes in the EE and CA countries, where up to 90% of infections are caused by subtype A, IDU-A variant[53,60,61]. Subtype B has been found as the second most common variant (~4%), followed by CRF03_AB and CRF02_AG, with CRF02_AG spreading rapidly in Russia and CA countries[53].

Most of these trends have been associated with the stable growth of the heterosexual route of HIV transmission (up to 50% of new infections) and the migration of individuals between the former Soviet Union countries and other regions[53]. However, the EE epidemic continues to be driven in large part by men who inject drugs[54], with growing evidence that sexual transmission to and from non-injecting partners could sustain a non-IDU HIV epidemic[62]. While most EE countries do now provide access to harm reduction services such as needle exchange programs and opioid substitution therapies, coverage is suboptimal. Where available, harm reduction services can curb the HIV epidemic considerably; an example is Ukraine, where, as a direct consequence of such services, the proportion of all newly registered HIV infections among

IDUs has declined steadily, from more than 42% in 2010 to 33% in 2013[54].

Although mother-to-child transmission (MTCT) rates are very low in Western Europe, management of birth and post-birth prophylaxis remains a priority and depends on resistance testing of the mother. In resource-limited countries, MTCT may represent a new generation of HIV transmission. If lost from surveillance, this generation has the potential to impact future HIV epidemics[3,51]. A systematic review of 91 studies analyzing the cost-effectiveness of HIV interventions in EE and CA revealed lower levels of resource mobilization for MTCT programs and other vulnerable categories, such as IDUs and sex workers, highlighting an additional area of unmet need[63].

In recent years, HIV subtype diversity has been growing due to the emergence of new genetic variants and the appearance of recombinant forms between "old-timers" and incoming viruses. A popular example is the emergence[64] and spreading[53,65] of CRF02_AG in CA countries, with the subsequent formation of a range of CRF02_AG/subtype A1, circulating, and unique recombinant forms[55,66]. The subtype-specific patterns of HIVDR in these viral genetic variants and associated transmission routes represent further knowledge gaps that should be addressed.

A vastly different HIV epidemic has been reported in Romania. The Romanian HIV-1 epidemic is characterized by the prevalence of the F subtype, which was shown in phylogenetic studies to have originated in the 1950s from the Democratic Republic of Congo and was separately spread by immigration waves to Brazil, Angola, and Romania[67]. Initially reported in the early 1990s, this subtype remained dominant during the following two decades, although recent years have seen the emergence of other subtypes[67]. In the overall HIV Romanian population, F1 accounted for 91% of strains in 2003-2011. In the IDU group, F1 decreased to 68.1% during 2011-2013, with 20.3% CRF14_BG and 5.8% B[68]. In this context, it is essential to follow the new infection waves and the spread of emerging subtypes in the Romanian population[67] and to develop further tools and algorithms to assess the likelihood of response to specific ART regimens in this particular patient population[69].

During an epidemiologic accident in the late 1980s, thousands of Romanian children were infected horizontally with HIV through healthcare-associated procedures[70]. This F1-dominant cohort, which had initially been initiated on AZT monotherapy and then transitioned to highly active ART as soon as it became available as a standard of care, is now considered "young by age, old by treatment," and is unique in Europe[38,67]. The 25-29 year age group forms by far the largest cohort among HIV-infected patients in Romania, totaling more than 6000 patients (data current through 2017). This is followed by those aged 40-49 years, while only 6% of infections are found in patients aged 24 years and under[71]. In Romanian patients, the main current transmission route is heterosexual (65% of cases diagnosed in 2017), followed by IDU (which saw a sharp increase in transmission after 2011; currently at 12%), MSM (19.5%), and other routes in smaller percentages, with MTCT remaining low, now at 1.6%[71].

Clinical practice in the region is adapting to the epidemic, and since 2001, Romania has adopted the policy of initiating ART in all patients living with HIV regardless of CD4 cell count, which was also introduced into the WHO guidelines in 2015[72]. However, diligent resistance monitoring and surveillance programs are needed to keep pace with evolving transmission characteristics to ensure the most appropriate management policies are in place.

An outbreak of HIV-1 subtype F has also been reported in the northwest of Spain[73]. This represents an entirely different epidemiology for the F subtype compared with Romania. The subtype is believed to be spreading among the local MSM population in specific regions of Galicia who are unaware of their HIV status and engaging in high-risk behavior. This is a distinctive situation given the rarity of F subtype in Western Europe. Furthermore, the rates of virologic suppression among individuals infected with subtype F in northwest Spain were found to be significantly lower than those among individuals infected with subtype B at multiple time points post-treatment initiation and were not related to ART regimen[74].

Asia

Gap 3: Limitations of current regional surveillance practices

The prevalence of TDRM in South Asian countries was recently investigated in the TREAT Asia Studies to Evaluate Resistance-Surveillance Study (TASER-S)[75]. In the TASER-S study, which recruited 451 treatment-naive, recently infected HIV-positive individuals from four urban locations across Asia, TDRM prevalence was 3.4% in Hong Kong; 4.7% in Bangkok, Thailand; 0% in Chiang Mai, Thailand; and 8.7% in Manila, The Philippines. While these levels are lower than those in West-

ern Europe and appear to be stable over time[75], in the absence of routine baseline genotyping or VL monitoring, they can still seriously compromise treatment effectiveness. This is increasingly problematic in developing Asian countries which rely heavily on the first-line generic drugs and have limited the second-line treatment options[76]. With 2016, the WHO guidelines recommending ART initiation in all individuals with HIV, regardless of CD4 count[51], further monitoring of HIVDR in individuals on ART, as well as regular surveillance of recently infected people should be encouraged[75].

In China, resistance monitoring was implemented across different areas of the country soon after the initiation in 2002 of the China Comprehensive AIDS Response Program to provide free HIV treatment[77]. Factors associated with the development of drug resistance include suboptimal treatment effectiveness, adherence problems, and delayed ART initiation. An analysis of three cross-sectional surveys conducted by the Chinese National HIVDR Surveillance and Monitoring Network and comprising 3667 patients from 31 provinces, 77% of whom were treatment-experienced, found that patients at high risk of HIVDR tended to receive care at township hospitals or village clinics, were from the Henan, Hubei, or Anhui provinces, had low baseline CD4 cell counts, were initiated on a didanosine-based regimen, and had missed doses in the previous month[76]. Nearly a fifth (19.2%) of treatment-experienced patients had resistance mutations, and 12.5% of those had TAMs. However, the large proportion of patients with virological failure and no resistance mutations suggests that treatment adherence is suboptimal and must be addressed[76].

The Henan province in China has drawn particular concern because of the extensive spread of HIV among former plasma donors, and the early implementation of ART in a population that was already likely to have drug-resistance mutations[77]. A large cross-sectional survey assessing HIVDR among 3235 patients in Henan who experienced first-line treatment failure identified multiple and complex HIVDR patterns and a high prevalence of TDR. NRTI, NNRTI, and PI resistance mutations were found in 50.26%, 63.12%, and 1.30% of patients, respectively. TAMs were also common in this patient cohort, and two typical TAM pathways with high resistance to all NRTIs were discovered: TAM-1 (M41L, L210W, and T215Y), with a prevalence of 8.96%, and TAM-2 (D67N, K70R, K219E/Q, and T215F) at 4.61%[77]. Timely virological monitoring through routine surveillance programs, introduction of baseline HIVDR testing, access to a wider range of ARVs, and treatment individualization are programmatic priorities in China's efforts to control HIV/AIDS in this and other, similarly difficult-to-treat patient cohorts[76,77].

Gap 4: Need to characterize the shift to sexual transmission within the MSM population

Studies have shown that TDRM prevalence is disproportionately high in the Asian MSM population[78]. Of the new infections recorded in China in 2014, sexual transmission accounted for 91.5% of cases, a quarter of which were homosexual. The fast increase in HIV infections in this risk group - from 2.5% in 2006 to 25% in 2014 - points to a shift toward sexual transmission among MSM in China[79].

Moreover, molecular epidemiologic surveys have shown a broadening of the HIV-1 subtype diversity in the MSM population. For example, the CFR01_AE strain, initially detected in heterosexual individuals, has overtaken subtype B in the MSM population, while the CRF07_BC strain, typically seen in the IDU risk group, has also been reported to be spreading among MSM[80].

Given the recent trends in the HIV epidemic among MSM in Asia, this group would particularly benefit from systematic efforts for the collection and assessment of HIVDR data, and interventions to control drug resistance[81].

Western europe

Gap 5: Limitations of current regional surveillance practices

The SPREAD analysis of newly diagnosed patients in Europe has demonstrated that the transmission of NRTI resistance is stable over time but higher in MSM than heterosexuals or IDUs, and in subtype B than in non-B subtypes. Viruses harboring single TDRM mutations were identified in 69% of people with TDR, and most frequently conferred NRTI resistance, 84.4% of which were TAMs (most commonly revertant mutations at 215 and M41L)[8,13,27]. The transmission of NRTI, NNRTI, and PI resistance mutations was found to be stable over time from 2002 to 2010, although they were present at a higher prevalence in patients with recent infection compared with those with an unknown duration of infection[27].

HIV subtype B is the most prevalent form in Europe, while subtype C predominates globally[37,82].

Subtype distribution is correlated with demographic parameters indicative of compartmentalization as defined by origin and social and individual behaviors[37]. For example, the high prevalence of subtype B in the

MSM population may be reflective of the high degree of compartmentalization of this population[37]. Resistance mutations in subtype B also occur in non-B subtypes but have the tendency to adopt subtle patterns; for example, V106A is frequently observed in subtype B viruses under selection by NNRTI, compared with V106M in subtype C[83,84]. There is also a greater tendency for subtype C to develop K65R against NRTI[85,86]. Efficient methods are available for sequencing viral subtypes[29] but problems exist with all approaches, and there is a need to optimize subtype sequencing.

Gap 6: Need for improved surveillance of integrase inhibitor resistance testing in naive patients

Monitoring resistance to integrase strand transfer inhibitors (INSTIs) is especially important in view of the recent updates to European guidelines, which recommend 2NRTIs + INSTI as first-line ART, including for post-exposure prophylaxis (PEP)[20]. In this context, surveillance data may guide issues such as the need to test for baseline INSTI resistance testing in ARV-naive patients[17].

A single mutation at position Y143, Q148, or N155 of the integrase gene can lead to raltegravir resistance[87], with a >10-fold reduction in susceptibility[17]. Raltegravir often selects for more than one INSTI-resistant lineage within a patient, indicative of a low genetic barrier to resistance. Although viruses belonging to the N155H pathway often emerge early following virological failure, they are replaced within weeks by viruses stemming from the Q148 and, less commonly, the Y143 pathways[17]. The resistance profile of elvitegravir is similar, and mutations at positions 148 and 155 were also observed in patients who failed treatment with the *quad* pill, a 1-pill-a-day regimen that contains cobicistat-boosted elvitegravir and two NRTIs[88].

In treatment-naive patients, second-generation INSTI, dolutegravir, appears to be the only ARV for which no emergent resistance has been detected, even after protocol-defined virological failure, although dolutegravir drug pressure has been shown to select for the R263K mutation[87,89]. The ability of dolutegravir to inhibit viral replication can also be decreased when mutations associated with HIV resistance to raltegravir and elvitegravir are combined with several other minor resistance mutations. Although more data and ongoing resistance monitoring are needed to confirm these findings, dolutegravir's unique ability to evade resistance may have relevance for public health strategies aimed at limiting HIVDR[87,89].

Gap 7: Surveillance of minority groups and the shift toward non-B subtypes

Resistance transmission has been associated with specific populations,[13] and surveillance efforts should be directed toward minority populations to better understand the dynamics of resistance in these groups.

The MSM population appears to be the primary driver of TDRM within Western Europe[90]. MSM were shown to have significantly higher TDRM prevalence compared to heterosexuals and IDU in an analysis of TDRM trends in the European SPREAD program[13]. This was confirmed by a national sentinel surveillance program of 661 newly diagnosed patients from France, in which MSM and B-subtype-infected patients were the groups with the highest TDRM rates[12]. Nevertheless, in the same study, the frequency of patients infected with the non-B virus subtype was found to increase over a decade, from 33.1% to 43.5%, while the proportion of CRF_02 (AG) viruses remained stable at approximately 20%. Sequences from the 661 viruses revealed 46 clusters, of which 29 gathered individuals living in the same geographical area[12].

Another French study revealed the spread of non-B subtypes in individuals of French origin, with particular involvement of MSM[91]. Of 233 recent HIV-1 infections with non-B variants identified between 2007 and 2010, 36.5% occurred in MSM and 39.5% were due to heterosexual transmissions. Of the 14 clusters identified, MSM were involved in 11, and the largest cluster involved MSM infected by a CRF02_AG variant[91].

The trend toward an increase in non-B subtype HIV infection has been observed across Europe. A study of 2208 treatment-naive patients from 19 European countries monitored from 1996 to 2002 found that even though drug-resistant variants were more commonly seen in patients infected with subtype B virus and were likely due to a longer exposure of these viruses to drugs, baseline resistance in non-B viruses increased from 2.0% (1/49) in 1996-1998 to 8.2% (16/194) in 2000-2001[92].

Taken together, these findings reveal a shift toward non-B subtype HIV resistance and provide a rationale for testing and monitoring of all drug-naive patients, with particular attention on minority groups. This is reinforced by the European guidelines for HIV, which state that initial treatment choice should be based on resistance testing in treatment-naive patients[20].

Gap 8: Lack of data regarding the impact of migration

With the predicted increase in migration to Europe from areas where surveillance programs are less

robust, immigrants infected with HIV pose an increasing source of transmission and TDRM. Surveillance data from countries of origin will provide a critical tool in preparing for the impact of such an influx on HIV transmission and subsequent management. However, data are scarce from regions such as Africa, from where large numbers of immigrants are expected. There has been a significant scale-up of ART in Africa over recent years, which has been coupled with a reported increase in the prevalence of drug resistance[93], but data remain sparse. Analysis of more than 13,000 patients from sub-Saharan Africa suggests a significant increase in drug resistance since ART has become available, driven by NNRTI resistance in east and southern Africa. Further, tenofovir resistance has been reported in more than 50% of patients failing first-line treatment in sub-Saharan Africa, compared with 20% in Europe[9,94]. With increasing prevalence of resistance to standard first-line therapies, countries that do not employ routine drug resistance or VL testing are vulnerable to increased risk of ART failure and transmission of resistant virus[50]. The migration of individuals from such populations to Europe threatens current management programs, and there is a need, therefore, for enhanced surveillance and data of HIV drug resistance in resource-limited settings to better inform policies globally.

Guidelines and training

2015 marked some important milestones in the development and alignment of HIV guidelines. In 2015, the WHO guidelines[72] feature updates in two key areas: first, initiation of ART in all people living with HIV at any CD4 cell count; and second, use of daily oral pre-exposure prophylaxis (PrEP) in people at substantial risk of HIV infection as part of combination prevention approaches. The two recommendations, made available on an early release basis, are aiming to support countries to meet the ambitious UNAIDS 90-90-90 targets and will require them to further accelerate their HIV responses in the coming years[72].

Furthermore, 2015 marked the alignment of all international guidelines - WHO[72], US Department of Health and Human Services[95], and the European AIDS Clinical Society (EACS)[96] - on the key issue of ART initiation in all people diagnosed with HIV.

Meanwhile, the local uptake and feasibility of guideline implementation varies greatly, especially in low-resource countries[97]. A projection of eligibility for and the number of people on ART in 97 countries from 2015 to 2020 indicates that countries are unlikely to meet the UNAIDS targets unless they adopt a test-and-offer approach and increase ART coverage[98]. In the absence of additional financial resources, the ready adoption of newer technologies, wider access to treatment, and use of lower-cost ARVs will prove essential in many parts of the world, as countries collectively move toward adopting the WHO 2016 guidelines. At a policy level, expanding ART eligibility to achieve the 90-90-90 targets will require the removal of a number of barriers, provision of necessary infrastructure, increased advocacy, and urgent exploration of healthcare system strengthening initiatives[98]. In this vein, the present review has identified a number of gaps in guideline implementation and training for those providing care to HIV-infected individuals around the globe (Table 3).

General consensus and guidance

Gap 1: Need for clear consensus guidelines and consistent terminology

While progress has been made within international guidelines on a number of topical issues of HIV management, local dissemination and implementation of guidelines diverge vastly. With updated guidelines recommending broad ART initiation in all HIV-infected individuals, the need for resistance testing is greater than ever; however, experts have warned against the over-medicalization of testing messages, which could lead to unnecessary stigmatization in some cultures[99,100]. In addition, in resource-poor regions that have traditionally not been part of the "treatment as prevention" discourse, such as EE and CA, testing should be integrated with broader local HIV prevention initiatives, including needle exchange programs and opioid substitution therapy[99,100].

In EE, for example, there is currently a low level of knowledge with regard to HIV testing and medical practitioners would benefit from broader dissemination of locally translated versions of the EACS guidelines and further training on using the guidelines to support everyday decision making (when to test/whom to test/how to interpret results).

In Asia, gaps exist in staff experience and training; provision and duration of ART; and availability of VL and resistance testing, which may impact the management of TDRM and ADRM. Patient education on the need for and feasibility of ART alongside harm reduction interventions is also necessary[99,100]. For example, a widespread concern among inmates coinfected with HCV is the likelihood of drug–drug interactions; similar

Table 3. Gaps in guidelines and training

Gaps: Guidelines and training
General consensus and guidance
1. Need for clear consensus guidelines and consistent terminology
Guidance on specific drug types and clinical scenarios
2. Guidance on the appropriate use of specific drugs in the setting of resistance
3. Inconsistent identification and management of low-level viremia
4. Need for consensus guidance on appropriate use of post-exposure prophylaxis

concerns have been voiced by those receiving methadone as opioid substitution therapy. Such issues need to be proactively addressed by health-care professionals to support treatment uptake and adherence.

Guidance on specific drug types and clinical scenarios

Gap 2: Guidance on the appropriate use of specific drugs in the setting of resistance

Although international guidelines are largely in agreement on the backbone of first-line ART, they show a lack of alignment with regard to relatively recently available ARVs such as dolutegravir and maraviroc. This is partly due to emerging clinical data on the effectiveness, safety, and potential for comorbidity reduction of these agents, but it also reflects whether guidelines are primarily intended for patients in low- or high-income countries. The feasibility, cost-effectiveness, and impact of immediate treatment for all people living with HIV, regardless of CD4 cell count, are currently evaluated at a population level in a number of ongoing implementation studies[51]. Aside from gathering conclusive evidence on novel ARVs, research priorities in this field include assessing the incidence of short- and long-term severe adverse events as a result of increased exposure to various drugs; identifying barriers to, and enablers of, adherence, and long-term retention in treatment; and evaluating the magnitude of the prevention benefit of early initiation of ART in key populations[51].

Gap 3: Inconsistent identification and management of low-level viremia

International guidelines also differ in their interpretation of and management recommendations for low-level HIV viremia (LLV). This is partly due to a dearth of clinical data on the subject and partly to a lack of consensus on the definition of treatment failure[101]. Notably, it has not yet been elucidated whether viral blips and LLV are associated with an increased risk of drug resistance and virological failure. Furthermore, there is no consensus on the optimal treatment selection in patients with LLV. While it has been hypothesized that PI-based regimens may lead to viral rebound and, therefore, persistent LLV, data comparing the outcomes of NNRTIs and PIs failed to find a difference, with treatment adherence possibly playing a role in LLV instead. Taken together, these findings highlight the need to synthesize the emerging evidence on the clinical, virologic, and immunologic consequences of persistent LLV/very LLV, and to harmonize guidelines around treatment selection for managing LLV, in particular, viremia of 50-200 copies/mL[101].

Gap 4: Need for consensus guidance on appropriate use of PEP

The WHO[102] and European[20] guideline recommendations on PEP have undergone recent changes. Conventionally, separate WHO and national guidelines had been developed for PEP, according to exposure type (occupational or non-occupational) and populations (adults or children). The new WHO PEP recommendations cover all types of exposures in all population groups including adults, adolescents, and children[102]. While the new guidelines also aim to simplify PEP prescribing and improve adherence by recommending better-tolerated drugs, local resources and access to care will affect the level of implementation.

A number of research areas will need exploring in PEP, including[102]:

- Understanding the barriers to accessing PEP for all population groups
- Assessing the feasibility of PEP delivery in various healthcare settings
- Resistance profiling and treatment selection, especially in light of the use of a low barrier to resistance agents now favored in PEP such as raltegravir
- Potential use of newer ARV drugs (dolutegravir, rilpivirine, elvitegravir, and maraviroc)
- Interventions for populations at high risk of poor adherence, managing PEP interruptions
- Strategies and impact of transitioning from PEP to PrEP.

Conclusions

In a previous review, the authors identified gaps in knowledge of the science and technologies of HIVDR in an effort to facilitate scientific exchange and ad-

vance the field through the optimal use of technology to detect and interpret resistance, and the subsequent selection of appropriate ART. This review focuses on surveillance of HIVDR from both global and regional perspectives, with discussion on gaps in policy, and implications for clinical practice and regional variation. Recent updates have seen the harmonization of international guidelines, but significant regional variability exists in epidemiology and clinical practice (as reflected by availability of resources and training). Vulnerable groups, in particular, have been identified as having unmet needs and efforts should be made to align surveillance and patient education programs to better address these groups.

Recent studies have demonstrated advancements in monitoring and surveillance,[4,10,13] but gaps still remain, in particular, in the utilization of representative sampling and of patients who fail therapy. As well as optimizing methodology, sampling of sufficient numbers to analyze predictors of failure will enhance future management of ART selection and switch. Coupled with that is the need for up-to-the-minute resources that detail current mutations and local data on regional epidemiology to ensure the most appropriate and clinically relevant information is available. Furthermore, standardization of protocols will facilitate the generation of data with intercenter comparability.

Although genotyping at the initiation of ART has a positive impact on patient outcome, this is not carried out routinely on a global scale[1,21]. At a regional level, there is a need to develop technologies that are affordable and implementable to promote this as a standard to care. Furthermore, on a regional level, there is a requirement to address the unmet needs of vulnerable and minority populations, particularly those in lower income countries, and to better understand the patterns of transmission and viral epidemiology to optimize future policy and surveillance.

Finally, it will be important to expedite resources and guidelines with current knowledge and data on new therapies and practices as they become available. Coupling this with consistency across recommendations will aid the global adoption of best practices.

Identified here are gaps in population monitoring and surveillance of HIVDR together with significant variation in regional practice and policies. Combined with the findings from our earlier review, addressing these gaps through scientific exchange and focused research will enhance our understanding of HIV and progress the optimized management of disease globally.

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Conflicts of interest

Dr. Bobkova reports a grant from the Russian Science Foundation, and personal fees from AbbVie, outside the submitted work. Dr. Boucher has received research grants from Merck and personal fees from AbbVie and ViiV Healthcare. Dr. Dorr is an employee of AbbVie and may hold stock; in addition, Dr. Dorr has a patent issued to AbbVie. Dr. Hung reports grants from Janssen and ViiV Healthcare; advisory board fees from AbbVie, Gilead Sciences, Janssen; and personal fees from AbbVie, Gilead-Sciences, and BMS, outside the submitted work. Dr. Kaiser reports personal fees from Gilead, AbbVie, Janssen, Roche, Siemens, ViiV Healthcare, and Alere, outside the submitted work. Dr. Marcelin has nothing to disclose. Dr. Streinu-Cercel reports a grant from AbbVie, personal fees from AbbVie, BMS, and J&J; and participation as principal investigator in trials for BMS, Gilead-Sciences, and MSD, outside the submitted work. Dr. van Wyk was an employee of AbbVie when this work was carried out and is a current employee of ViiV Healthcare. Dr. Vandamme reports personal fees from AbbVie and Gilead, outside the submitted work; and spouse is receiving consultancy fees from AbbVie, Gilead, and ViiV Healthcare.

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