Global HIV Antiretroviral Drug Resistance: A perspective and report of an NIAID Consultation

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Antiretroviral therapy (ART) is widely recommended for all infected with HIV. The importance of wide population coverage and effective suppression of viremia is reflected by the 90-90-90 goals established by the Joint United Nations Programme on HIV and AIDS.   HIV prevention strategies increasingly have antiretrovirals, including pre-exposure prophylaxis as a core component. Acquired and transmitted HIV drug resistance may compromise effective control of HIV. High resistance rates in children and in communities with mature treatment programs, poorly documented rates in populations most at risk for both HIV infection and treatment failure and delays in switching regimens after documented virological failure suggest that current strategies to minimize HIV drug resistance are sub-optimal. Factors that might mitigate these trends include the adoption of more forgiving regimens and technologies that could be deployed to identify treatment failures early. In May 2016, the Division of AIDS at the United States National Institutes of Health (NIH) convened a consultation to identify research gaps and characterize ways in which the research community might support efforts to address global HIV drug resistance. This Perspective outlines the conclusions of the group and is the introduction to a supplement to this journal outlining some of the major challenges and research gaps associated with HIV drug resistance globally.

HIV drug resistance is associated with sub-optimal virological suppression, subsequent immunologic decline, and poor clinical outcomes [1]. Maintaining a failing regimen leads to accumulation of resistance mutations, compromising the efficacy of subsequent regimens [2]. Viral load (VL) monitoring has been embraced by treatment programs and by recommending authorities because early identification of virological failure may reduce acquired HIV drug resistance. Nevertheless, significant challenges with VL scale up persist: access to VL testing remains limited in many countries, results are returned slowly to clinicians and action on these results is often lacking [3]. Insufficient training together with the requirement in many countries for a confirmatory VL in order to obtain alternative regimens compounds delays in treatment switch.   For example, in 2015, the Kenyan Ministry of Health

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documented more than 110,000 VL measurements over 1000 HIV RNA copies per milliliter (c/ml); only 2.1% represented confirmatory VLs [4]. These data, in addition to national program and procurement data, suggest a gap in the numbers of patients needing to switch therapy compared to the frequency of those who actually switch. Treatment programs struggle with diverse, often inadequate data sources to estimate ART use and future needs, leading to incorrect forecasting and interruptions of drug supply.

As treatment programs develop, the prevalence of pretreatment resistance increases, and very high rates of resistance-associated mutations have been documented in several countries and in specific populations. The rate of increase also rises. For example, in East Africa, while the overall resistance level is 7.4%, 8 years after roll out, the rate of increase of any transmitted drug resistance mutation is estimated at 29% per year [5]. Models suggest that if pretreatment resistance exceeds 10%, the goal of 90% virological suppression will not be met [6]. HIV drug resistance may also compromise incidence goals: individuals with high VLs are more likely to transmit HIV to their partners [7].

Some populations have extremely high drug resistance rates. Rates of drug resistance in perinatally-infected children have been reported at 10-24%, but increasing to 34-56% in patients with prior exposure to drugs to prevent maternal to child transmission [8]. This, combined with higher VL and limited ART regimens contribute to rates of virologic failure that are higher in HIV-infected children compared to adults, especially with non-nucleoside reverse transcriptase inhibitor-based regimens [9]. High rates of both acquired and pretreatment drug resistance have been observed in adult populations most at risk for HIV such as men who have sex with men, commercial sex workers and injection drug users in Latin America and the Caribbean [10], in sub-Saharan Africa [11] and in Asia [12]. Although the exact dynamics of the spread of drug resistant virus is unknown, phylogenetic approaches demonstrate that drug resistance can spread from ART-experienced and naïve individuals to others. If the resistance

mutation transmitted is one that confers resistance to the agents used for pre-exposure prophylaxis, this may compromise HIV prevention efforts and incidence goals.

The World Health Organization (WHO) has suggested several monitoring activities for HIV drug resistance assessment in low and middle income countries () in an effort to obtain nationally representative data on HIV drug resistance. These include monitoring of clinic-level early warning indicators, surveys of pretreatment HIV drug resistance in populations initiating ART, surveys of acquired HIV drug resistance, and surveys in infants less than 18 months. Early-warning indicators include variables such as on time pill pickup, retention on ART at 12 months, drug supply shortages, VL testing and VL suppression with the latter three also being President's Emergency Plan for AIDS Relief (PEPFAR) indicators; countries receiving PEPFAR funds are required to report these data[13]. WHO recommends yearly monitoring of early warning indicators followed by representative national surveys every three years.   Few countries have successfully implemented this recommendation. The number of nationally-representative surveys peaked in 2012 but has dropped significantly since then, resulting in a paucity of new data in the published literature.

During the NIH consultation four broad themes with specific knowledge gaps were identified.

1. Surveillance needs are significant and the declining number of nationally representative HIV resistance surveys is concerning. Sampling methods for current national surveys may not capture pockets of resistance in key populations and geographic areas. Innovative approaches that simplify collection of data on community VL and community drug resistance will improve national and international surveillance efforts. Advanced technologies such as multiplex next generation sequencing methods could yield robust surveillance tools to simplify surveillance activities if they can be implemented for surveillance in low and middle income countries. Beyond surveillance, there is the opportunity to develop platforms that combine these data with

clinically useful patient-level data. These new technologies could also generate

phylogenetic/phylodynamic data that could be used to target prevention interventions in

specific populations [14, 15]. Electronic capture of data and cloud-based harmonization of

various data streams may help capture this data in usable forms[16].

2. Research is needed to further understand the effects of currently used antiretroviral agents in

   individuals with non-B subtypes, especially the effects of HIV drug resistance mutations when

   combined with previously acquired mutations. The introduction of dolutegravir and tenofovir

   alafenamide may have dramatic effects on reducing the development of HIV drug resistance in

   low and middle income countries; some of these effects may be related to viral subtype.

   Research has demonstrated that resistance mutations present at low levels within the HIV

   quasispecies (minor variants) may predict treatment failure [17, 18]. When sensitive assays are

   used that detect minor variants, rates of transmitted resistance are significantly increased in low

   and middle income countries [19, 20] Better methods to detect and use these variants for

   clinical care are needed. Some studies have suggested that NRTIs retain partial activity even in

   the presence of resistance-associated mutations [21]. Improved genotype-phenotype

   correlations are needed to better understand when NRTIs need to be switched. Simplified

   regimens of less than three drugs may also be possible with newer agents (e.g. dolutegravir +

   3TC), but the effect on HIV drug resistance needs to be investigated. Long-acting regimens may

   prove useful in populations where adherence is problematic, but the HIV drug resistance

   implications require study. Most low and middle income countries use a VL cutoff of 1000 HIV

   c/ml as the definition of virologic failure, but studies are needed to determine if assays using

   lower cutoffs are feasible and would help prevent HIV drug resistance in low and middle income

   countries. Studies need to be conducted not only in adults, but also in children.

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3. In the medium term individualized or stratified regimen modifications are needed for specific populations and communities. Simplified testing that combines VL with HIV drug resistance testing in different specimen types will allow for rapid identification of virological failure and adjustment of therapy, if required. Point-of-care or near-point-of-care diagnostics may improve the clinical management of individuals at risk for HIV drug resistance at initiation of therapy or at failure. Studies are needed to determine how best to deploy these approaches.

4. Programmatic and other non-research data sources should be harmonized and improved to allow for the evaluation of interventions in service delivery and models of care on the development of HIV drug resistance. Simplified, electronic data collection methods will allow for rapid evaluation of interventions and the effect of specific HIV drug resistance trends on long term outcomes. If proxies for specific HIV drug resistance data, such as community VL, are used these measurements should be tested and validated. Modeling and cost-effectiveness evaluations will be needed to understand the economic impact of newer agents.

Conclusion

Research initiatives are focused on collecting the best evidence from a variety of sources to drive policy decisions for the prevention of HIV drug resistance. Newer antiretroviral agents with a higher barrier to resistance will become available in the near future, but caution should be exercised when assuming that these agents will solve the HIV drug resistance problem. As test-and-start strategies are considered, data to support optimal first line therapy will be required. In the near future patient level HIV drug resistance assessment will be needed in specific populations, especially those requiring third-line regimens. Finally, the contribution of pre-exposure prophylaxis to the overall resistance burden is unknown , but is concerning given that the failure of pre-exposure prophylaxis in the setting of HIV drug resistance has been described.

Attention to HIV drug resistance, as guided by the WHO, will be important in achieving the

milestones that will end the HIV epidemic.

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