The Impact of HIV Drug Resistance on the Selection of First- and Second-Line ART in Resource-Limited Settings

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At the end of 2011, more than 8 million people were receiving antiretroviral therapy in low- and middle-income countries, a dramatic 26-fold increase from December 2003 [1]. Although it can be minimized, some degree of human immunodeficiency virus (HIV) drug resistance is anticipated to emerge among people on treatment even when appropriate antiretroviral therapy is provided and high levels of adherence are achieved. Monitoring HIV drug resistance is critical for optimal program management due to its important policy implications. Data on HIV drug resistance provide the basis for selecting future first-line treatment regimens, identifying the most effective second-line therapies for patients failing first-line combinations, and for selecting optimal approaches for preventing mother-to-child transmission of HIV, as well as for pre- and post-exposure prophylaxis.

While considerable research and analysis exist on the implications of HIV drug resistance for treatment management in high-income countries, these issues have been less comprehensively assessed in resource-limited settings. This is a critical knowledge gap, particularly as antiretroviral programs mature and important differences in the management and delivery of antiretroviral therapy (ART) in both settings do not allow for the direct application of standard policy responses. For example, in contrast to the individualized patient management model adopted in high income settings such as Europe and North America, most low- and middle-income countries have embraced a public health approach to HIV treatment, based on one standardized first-line therapy for all patients initiating ART and a second-line regimen for patient failing therapy [2]. This implies that, while a wide armamentarium of drugs is typically available in rich countries, often there are only limited or no opportunities for individualized therapy based on resistance testing results. Moreover, viral load testing is currently not generally available in most low- and middle-income countries, and therapeutic monitoring is often performed using clinical and CD4 lymphocyte cell count criteria.

With the purpose of improving the available knowledge on the implications of HIV drug resistance for ART management in low- and middle-income countries, the World Health Organization (WHO) and CHAIN—the Collaborative HIV and Anti-HIV Drug Resistance Network, a consortium of 26 partners institutions with broad-based expertise on HIV drug resistance research—organized a consultation in Geneva, Switzerland, in October 2012 to discuss the topic, “Impact of HIV Drug Resistance on the Selection of First- and Second-Line ART in Resource-Limited Settings.” The workshop brought together over 50 experts with the objective of reviewing the growing evidence base on HIV drug resistance and discussing its impact.
for the use of antiretrovirals (ARVs) within a public health approach. This supplement summarizes the 8 plenary presentations discussed at the meeting.

**MAGNITUDE OF HIV DRUG RESISTANCE IN LOW- AND MIDDLE-INCOME COUNTRIES**

A major effort has been undertaken to monitor drug resistance in the context of antiretroviral rollout. In 2004, WHO initiated global surveillance of HIV drug resistance to adequately monitor the emergence and transmission of HIV drug resistance [3]. Of 72 WHO surveys of transmitted drug resistance conducted between 2004 and 2010, 20 (28%) were classified as having moderate (between 5% and 15%) prevalence of resistance. With respect to acquired HIV drug resistance, according to data from 36 WHO conducted in 12 low- and middle-income countries between 2007 and 2010, the overall prevalence of HIV drug resistance to any drug among people starting antiretroviral therapy ranged from 4.8% (95% confidence interval [CI], 3.8%–6.0%) in 2007 to 6.8% (95% CI, 4.8%–9.0%) in 2010. About 90% of patients alive and on therapy at 12 months achieved viral load suppression. Among people with virological failure, 72% had resistance, mostly to nucleoside reverse transcriptase inhibitor (NRTI) and nonnucleoside reverse transcriptase inhibitor (NNRTI) drugs [4].

These data carry important implications for the selection of optimal antiretroviral combinations. Hosseinipour et al in “Emergence of HIV Drug Resistance During First- and Second-Line Antiretroviral Therapy in Resource-Limited Settings” review published data on the emergence of HIV drug resistance among individuals failing first-line therapy, as well as clinical and resistance outcomes of those receiving second-line therapy in selected resource-limited settings. Resistance surveys among patients initiating first-line NNRTI-based therapy found that between 76% and 90% of patients alive on therapy achieved HIV RNA suppression at 12 months. Among those with detectable viral loads, 60%–72% had HIV drug resistance identified. Nevertheless, most cases involved primarily M184V and NNRTI mutations, which preserved most of the activity of proposed second-line regimens.

What does this ultimately mean for patient outcomes? Rapid emergence of virological failure and accumulation of resistance mutations among first-line therapy failures may compromise not only second-line regimen response, but can equally lead to the transmission of drug-resistant HIV to newly infected individuals. This could compromise the long-term effectiveness of currently available first-line regimens. In addition to informing ART policy, mathematical modeling can also be instrumental to better understand the impact of HIV drug resistance on patient outcomes. In “Transmission of Drug Resistant HIV and Its Potential Impact on Mortality and Treatment Outcomes in Resource-Limited Settings,” Cambiano et al estimate the potential long-term impact of transmitted HIV drug resistance (HIVDR) on mortality in people on ART by comparing the predicted mortality rates over 45 years with a theoretical counterfactual scenario in which transmitted drug resistance (TDR) does not occur. The impact of eliminating HIVDR is estimated to be limited if prevalence of TDR at baseline is below 10%. However, in situations where TDR is higher (above 20%) it is estimated that future mortality on ART would be up to 18% higher than if resistance mutations were not transmitted.

**IMPLICATIONS OF HIV DRUG RESISTANCE FOR FIRST- AND SECOND-LINE THERAPY CHOICE IN ADULTS AND CHILDREN, AND FOR PREVENTION OF MOTHER-TO-CHILD TRANSMISSION**

In addition to its overall impact on survival and mortality, the transmission and emergence of HIVDR carries important program implications with respect to the choice and sequencing of antiretroviral drugs for the treatment of both adults and children, and for the implementation of interventions to prevent mother-to-child transmission of HIV.

In “Antiretroviral Treatment Sequencing Strategies to Overcome HIV Type 1 Drug Resistance in Adolescents and Adults in Low-Middle-Income Countries,” De Luca et al assess and discuss the optimal ART sequencing options in resource-limited settings based on currently available drugs and treatment monitoring opportunities. From the drug resistance point of view and based on the limited virologic monitoring available in low- and middle-income countries, the authors suggest that the optimal sequencing includes the use of a tenofovir-containing NNRTI-based first-line regimen, followed by a zidovudine-containing, protease inhibitor (PI)–based second-line. Other options and their consequences are explored by considering within- and between-class sequencing opportunities, including boosted-PI monotherapies and future options with integrase inhibitors.

An additional topic of great programmatic relevance refers to the recommended phasing out of stavudine in first-line treatment due to its serious long-term toxicities [5]. As countries design and implement stavudine phase-out strategies, they must carefully consider what course of action is more likely to ensure continued viral suppression and optimal patient outcomes. Tang et al review this issue in “Nucleoside Reverse Transcriptase Inhibitor Resistance Mutations Associated with First-Line Stavudine-Containing Antiretroviral Therapy: Programmatic Implications for Countries Phasing Out Stavudine.” The article reviews 35 publications describing NRTI-resistance mutations associated with first-line stavudine-containing regimens, and found that regardless of the combination of concomitant NNRTI, duration of therapy, or subtype, tenofovir was more likely than zidovudine.
to retain antiviral activity against viruses emerging from a first-line stavudine-containing regimen.

Although available evidence in low- and middle-income countries indicates that increases in the prevalence of transmitted drug resistance have primarily been NNRTI-related, a concern remains that NRTI resistance associated with exposure to NNRTI-based first-line regimen could compromise the NRTI backbone and the overall effectiveness of second-line regimens. In “Resistance at Virological Failure Using Boosted Protease Inhibitors Versus Nonnucleoside Reverse Transcriptase Inhibitors As First-Line Antiretroviral Therapy—Implications for Sustained Efficacy of ART in Resource-Limited Settings,” Hill et al examine whether boosted protease inhibitors in first-line regimens might be better at protecting against the emergence of NRTI resistance mutations when compared to NNRTI-based first-line regimens. The authors conclude that due to the equivalent efficacy and more favorable resistance implications of boosted PI–based versus NNRTI-based regimens, boosted PI–based first-line therapy could in the future be considered as an option once new drugs from other classes become available as second-line alternatives in resource-limited settings. Currently, the implementation issues associated with PI–based first-line therapy are still considerable, indicating that widespread use of PI–based first-line therapy is neither warranted nor feasible at this time, due to the lack of easy-to-use, once-daily fixed-dose combination formulations, drug interactions, superior cost, and the predicted increase in the risk of resistance-related failure of NNRTI/NRTI second-line regimens. These considerations reinforce the need to promote optimal adherence and retention in care, and program functioning to maximize the effectiveness of first-line NNRTI-based regimens.

In addition, resistance will be minimized if virological failure is detected in a timely manner, indicating the importance of scaling up methods for virological monitoring.

The specific aspects related to HIVDR in vertically infected children are discussed by Fitzgerald et al in “Development of Antiretroviral Resistance in Children With HIV in Low- and Middle-Income Countries,” particularly with respect to the prior exposure of vertically infected children to antiretrovirals in the context of prevention of mother-to-child transmission or ART taken by the mother during pregnancy and breastfeeding. The authors review available evidence to optimize first- and second-line ART regimens in these situations, and discuss issues related to adherence to therapy during childhood, including availability of appropriate drug formulations, pharmacokinetics, and administration of ART by caregivers. They also consider ways to improve sequencing of drugs and regimens across different ages in childhood to minimize toxicity and prevent the development of drug resistance.

Related to this issue, Paredes et al review, in “Impact of Antiretroviral Drugs in Pregnant Women and Their Children in Africa: HIV Resistance and Treatment Outcomes,” the impact of the different approaches to prevent mother-to-child transmission of HIV (Option A, B, B+) on the emergence of drug resistance and on the efficacy of future first-line ARV therapy. This is particularly important not only to minimize HIVDR for mothers and their infants, but also to support the achievement of the goal of eliminating new pediatric HIV infections by 2015 and improving maternal, newborn, and child health and survival in the context of HIV [6].

As scientific evidence regarding the potential preventive benefits of antiretroviral therapy grows, increasing consideration is being given to expanding the use of antiretrovirals for HIV prevention, both by people living with HIV to reduce HIV transmission (TasP) and as preexposure prophylaxis by HIV-negative individuals to reduce HIV acquisition (PrEP). Although promising, concerns have been raised with respect to the impact of such strategies on HIVDR emergence, particularly with respect to the concomitant use of coformulations using tenofovir in both antiretroviral therapy and ARV-based prevention strategies.

Gupta et al explore these issues in “OralAntiretroviral Drugs as Public Health Tools for HIV Prevention: Global Implications for Adherence, Drug Resistance, and the Success of HIV Treatment Programs.” While real and legitimate concerns exist about ART adherence and drug resistance in the context of PrEP and TasP in real-life settings, the authors argue that efforts aimed at HIV prevention through the use of these novel prevention strategies should go forward. Nevertheless, efforts must be made to monitor ART adherence and to intervene through counseling and other means in order to optimize adherence and retention in care, whenever necessary.

**LOOKING FORWARD**

This supplement provides a comprehensive evaluation of the implications of HIV drug resistance for the management of antiretroviral therapy in low- and middle-income countries, and indicates approaches to minimize resistance emergence and its transmission. Although still relatively contained, levels of drug resistance have been slowly increasing in many low- and middle-income countries since 2003, and the impressive reductions in mortality, morbidity, and incidence observed in many settings may be jeopardized if such trends are left unchecked.

Optimizing adherence, continued resistance surveillance, and improving treatment monitoring are critical for the long-term prevention of drug resistance. Although HIV drug resistance data from low- and middle-income countries are increasingly available, the limited surveillance data over time substantially limits the ability to assess trends in these countries. Future surveillance of transmitted and acquired HIV drug resistance should be enhanced to optimize program planning and management and to inform antiretroviral therapy policy.

This supplement also highlights the important additional reductions in mortality that could be achieved by minimizing the...
emergence and transmission of HIVDR. Currently, the lack of extensive and routine viral load monitoring in most low- and middle-income countries prevents the timely identification of treatment failure, thus resulting in the continued accumulation of resistance mutations that could significantly reduce the activity of next-line alternatives. WHO has since 2010 recommended that countries scale up viral load testing to improve the identification of treatment failure [5]. By optimizing regimen sequencing, viral load monitoring also promotes more effective and durable ART. This is particularly relevant as ART is increasingly initiated at an earlier stage and patients are expected to be on treatment for longer.

Issues such as cost and complex infrastructure requirements have so far prevented most countries from incorporating viral load monitoring in their standard ART monitoring protocols. However, as new, cheaper point-of-care technologies become available, it is possible to envisage the rapid scale up of viral load monitoring in low- and middle-income countries in the near future, particularly in settings with high ART coverage levels, where initial ART cohorts have already been on treatment for many years. It is important that partners be adequately prepared and resourced to assist with this process.

At 54%, the coverage of antiretroviral therapy in low- and middle-income countries must be considerably increased if the international community is to meet its target of achieving universal access to antiretroviral therapy by 2015 [7]. As the accomplishments of the past decade demonstrate, this goal is certainly within our reach, but the twin successes of treatment scale up and resistance containment depend on the collective effort of researchers, activists, program managers, and policy makers, with strong management, accountability, communication, advocacy, and resource mobilization required at all levels. By helping address an important knowledge gap and highlighting areas where additional research is needed, we hope this supplement will help further enhance the management and treatment of HIV infection, particularly in low- and middle-income countries, and ultimately result in longer and better lives for all people living with HIV.

Notes

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