Emerging HIV Drug Resistance in the Resource-Poor World: Challenges and Strategies

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Determining Factors of Anti-retroviral Drug Resistance

At the end of 2011, more than 8 million People Living with HIV (PLWH) were receiving Anti-retroviral Therapy (ART) in low- and middle-income countries [1]. Accordingly, the advent and extensive use of Highly Active Anti-retroviral Therapy (HAART) has dramatically reduced the mortality and morbidity associated with the HIV infection worldwide [2]. However, many factors such as missing doses of medications, interruptions in ART and mono-therapy in the pre-HAART era may ultimately result in clinical drug resistance and virologic failure [3-8].

Many virological, immunological and pharmacological factors may play role in the development of Anti-retroviral Drug Resistance (ADR). First, the rate of viral duplication and turnover associated with HIV infection is too high [4,9-11]. In addition, circulating viral quasi-species may be extremely heterogonous. In fact, the lack of proofreading and an infidel reverse transcriptase can give rise to a genotypically heterogonous horde of circulating viral quasi-species soon after the infection has been established [12,13]. It is noteworthy that developing ADR requires accumulation of genomic changes within host bodily systems [4,14-18]. The consequent genetic diversity may result in the phenotypic drug resistance to various ART agents. Therefore, HIV shows unpredictable patterns of drug resistance *in vivo*, mainly due to its different adaptation mechanisms to local cellular environments, drugs' varying selective pressure, immune system reactions and many other virologic factors [19,20].

The wide availability of HAART may also be associated with the emergence of new HIV variants with less sensitivity to anti-retroviral drugs. Correspondingly, some authors believe that the evolution of ADR is an inevitable consequence of extensive HAART administration. For instance, *Palumbi* claimed that the extensive uses of prescribed regimens are accelerating retroviral evolutionary patterns toward the selection of mutant variants, especially in developed nations [21]. On the other hand, if HAART is discontinued in a patient who has developed drug resistance, the resistant mutants will be replaced with the wild type viral strain as a result of omitting drug selective pressure. However, there may be a chance to find a minority of drug resistant mutants by allele-specific Polymerase Chain Reaction (PCR) among such patients. By initiating the subsequent therapy that can seemingly induce a complete suppression in the viral load, the resistant mutants may persist at low levels in long-time infected cells [22-27].

Non-adherence or low-adherence of patients to ART regimens should also be noted as a determining factor of ADR. Also, limited access to HAART in non-industrialized nations and lack of optimal therapy after a previously failed treatment attempt have been reported as establishing factors of ADR worldwide. Many ADR infections have resulted from mono-therapy with only one specific drug type especially in the developing nations [23,26,28-30].

Prevalence and Global Trends of ADR

The World Health Organization (WHO) has reported that the prevalence of HIV drug resistance has been around 7% between the years 2003 and 2010 worldwide. With the expansion of ART coverage achieved over the last years, increasing prevalence of HIV drug resistance has been reported, particularly to Non-Nucleaoside Reverse Transcriptase Inhibitors (NNRTI) [31-33]. Reports suggest that 10-17% of naïve HIV patients in Australia, Japan, United States and Europe are infected with resistant viral strains to at least one of the ART agents [1,25].

In addition to the previous studies, many other surveys have been conducted to report the prevalence of ADR worldwide [34,35]. In general, the prevalence of transmitted HIV drug resistance (TDR) has shown an increasing trend in the developed world [36]; however, recently conducted surveys in Western Europe and United States have shown that the trend of TDR has become steady after its ascending pattern in such regions of the world [37-39]. The increasing efficacy of HAART and the development of new generation ARV agents have been proposed as possible reasons for this trend [40-42]. In a study conducted in a private clinic in San Francisco, the authors documented stable prevalence of ADR between the years 2004 to 2006. HIV drug resistance was associated with being MSM (Men who have Sex with Men), positive history of Sexually Transmitted Infections (STI), mono-therapy and the use of NNRTIs. Based on this survey, the overall prevalence of ADR during the three years was 13% [33].

Based on previous reports from some developed countries, single resistance mutations might be transmitted to almost 10-15% of the newly infected patients [43,44]. Although there is paucity of data about TDR trends in many developing nations, future therapeutic options might be highly limited due to the transmission of multi-drug resistant variants in such regions. In a survey performed in Spain during 1996-2010, TDR prevalence was 9.7% (10.6% for Spanish, 8.4% for Sub-Saharan Africans (SSA) and 7.9% for Central-South Americans (CSA) [36]. Regarding each region, the highest prevalence rates were found to Protease Inhibitors (PI) in Spanish (3.1%), to NNRTI in SSA (6.5%) and to NRTI in both Spanish and SSA (6.5%) patients.

Generally, the global TDR rate has shown a decline from 11.3% in 2004-2006 to 8.4% in 2007-2010 periods, especially among developed nations [36].Thereby, there has been a decrease in the rate of transmitted NNRTI and PI resistance over time within the developed

world [29,34,35]. However, a recent review of ADR among Asian countries revealed that there is no convincing evidence supporting the idea that TDR is gradually increasing in developing Asian nations [45]. Additionally, many countries -either developed or developing- have undertaken steps in order to increase the accessibility of HAART; nevertheless, with emerging drug resistance they have shifted the applied regimens. Although such approach has facilitated the stalling of ADR development, it has been accompanied by a considerably high expenditure of resources. Nonetheless, maintaining a low-level of ADR in developed countries might be closely related to its control in the developing world [34,36].

Strategies Adhered by the Developed World

In order to combat the developing ADR, various strategies have been implemented worldwide, most of which focus on the increasing patients' adherence. Also, developed nations have most recently applied the widespread use of drug resistance genotyping to support case management and treatment monitoring [37]. Although genotyping is expensive and requires certain facilities, the monitoring of patients is comparatively efficacious and may be successfully used to timely identify the gaps in service delivery in order to take the corrective action and minimize the emergence of ADR. In addition, most of these reports mentioned that ADR is higher among infrequently monitored patients compared to patients that are more intensively monitored [26,38]. Table 1 briefly shows the specific strategies that have been adhered by the developed world in order to combat emerging ADR according to the conducted surveys.

Application for the Resource-poor World

In order to identify the policies and strategies which stall the development of ADR in the developing world, we should bear in mind that many ADR determining factors in the developing settings may be dissimilar to that of the developed world. For example, the societal determinants such as migration, incarceration, epidemiology of addiction or other high risk behaviors or even the dispersal of most-

at-risk populations extensively vary among the two worlds. Thereby, one may conclude that most of the effectively implemented policies in the developed world may not be comparatively applicable within the developing world. In this regard, genotyping surveillance systems and tight patient monitoring may not be ideally applicable especially in circumstances were HIV is prevalent and lack of sufficient healthcare workers exists. For example, studies have debated the applicability of baseline resistance testing in Asian settings [45]. In fact, ADR in the developing world seems to be best brawled back by conducting simple strategies that most likely target the behavioral components and primary healthcare infrastructure. For example, reports indicate that unregulated or poorly supervised ART programs may result in the rapid ADR development among resource-poor nations. Budgetary and logistical problems further complicate the delivery of adequate ART regimens and induction of sufficient viral suppression. Correspondingly, interventions that increase the knowledge with regard to the importance of adherence and behavioral amendments (i.e. consistent use of barriers) among patients are of utmost importance under such circumstances [45]. Additionally, adoption to appropriate drug regimens as the first-line therapy would be extremely important to prevent development and transmission of ADR. Also, switching to second-line treatment combinations seems to be effective for the majority of patients failing first-line therapy [40]. Moreover, viral load monitoring (VLM) can be used as an indicator for treatment switch after the first regimen failure. Reduced resistance in those with frequent monitoring suggests that VLM not only detects poor adherence, but also can detect the gaps in service delivery and program performance [38]. In conclusion, the lessons learnt from the evolution and monitoring of ADR phenomenon in the developed world indicate that simple long-term strategies might be more effective if implemented focusing on patients' adherence as well as increasing ART access for all PLWH. Amending primary healthcare infrastructure and conducting simple ADR surveillance systems parallel to the administration of appropriate drug regimens as the first-line therapy are necessary to prevent the

Authors	Declared/Assessed Strategies	Country and Date
Shafer RW et al. [26] Dybul M et al. [46]	Switching the classes of drugs as the first reaction to resistance and Applying resistance assays to avoid unnecessary drugs administration.	USA, 2002- USA, 2002
Clavel F et al. [4] Cvetkovic RS et al. [47] Di Giambendetto S et al. [48] Shafer RW et al. [26]	Applying new drugs, for salvage or rescue therapy, that can be achieved by using agents with increased potency or better pharmacokinetic properties or by using novel classes (i.e. fusion inhibitors) which are not susceptible to cross-resistance.	France, 2004- New Zealand, 2003- Italy, 2009- USA, 2002
Buendia P et al. [28]	Predicting the development pathways of drug resistance with genotype-based prediction computer systems by using the patient's clonal (pyro-) sequences at the beginning of therapy and failure points	USA, 2009
Ji H et al. [49]	Selecting the best drug combination for national treatment programs by determining the prevalence of drug resistance mutations in both protease and reverse transcriptase inhibitors through using Pyro-sequencing	Canada, 2010
Yebra G et al. [36]	Conducting specific drug resistance surveillance tools among immigrants in order to prevent probable therapeutic failures, especially to NNRTIs.	Spain, 2011
Trevino A et al. [50] Imaz A et al. [51] Tang MW et al. [52]	Recommending not to apply commercial drug resistance tests before starting drug therapy, but to apply them at failure points, in order to increase the success rate of subsequent salvage therapy based on appropriate drug combination.	Spain, 2011-Spain, 2012-USA, 2012
Bercoff DP et al. [53]	Identifying the component of viral genome which can potentially evolve resistance properties against an agent for determining the more vigorous therapeutic options	Belgium, 2010
Truong HM KT et al. [32] Temereanca A EL et al. [[54] Vercauteren J WA et al. [41] Pingen M et al. [55]	Using genotyping resistance testing in ARV-naïve HIV positive patients; in order to identify regimens with vigorous genetic barrier to prevent failure of first line therapy.	Netherland, 2011-Europe and Israel, 2009-Romany, 2011-USA, 2011

Table 1: Some of the recently published studies that have targeted the efficacy and plausibility of various strategies in the era of anti-retroviral drug resistance in the developed world are presented.

evolution of ADR under such circumstances.

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