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Rates of emergence of HIV drug resistance in resource-limited settings: a systematic review

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Abstract

Background—The increasing availability of anti-retroviral therapy (ART) has improved survival and quality of life for many infected with HIV, but can also engender drug resistance. This review summarizes the available information on drug-resistance in adults in resource-limited settings (RLSs).

Methods—The online databases PubMed and Google Scholar, pertinent conference abstracts, and references from relevant articles were searched for publications available before November 2011. Data collected after ART roll-out were reviewed.

Results—Seven studies fulfilled the criteria for the analysis of acquired drug resistance while 22 fulfilled the criteria for the analysis of transmitted drug resistance (TDR). Acquired resistance was detected in 7.2% of patients on ART for 6–11 months, compared to 11.1% at 12–23 months, 15.0% at 24–35 months, and 20.7% at 36 months. Multi-class drug resistance also increased steadily with time on ART. The overall rate of TDR in all resource-limited countries studied was 6.6% (469/7063). Patients in countries in which ART had been available for 5 years were 1.7 times more likely to have transmitted drug-resistance than those living in a country where ART had been available for <5 years ($p<0.001$). The reported prevalence of transmitted HIVDR was 5.7% (233/4069) in Africa, 7.6% (160/2094) in Asia, and 8.4% (76/900) in Brazil.

Conclusions—The emergence of drug resistance following access to antiretroviral therapy in RLSs resembles what was seen in resource-rich countries and highlights the need for virologic monitoring for drug failure, drug resistance testing, and alternative drug regimens that have proven beneficial in these resource-rich settings.

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Authors' contributions

Kathryn Stadel performed the literature search, data extraction, data analysis, and wrote the first draft of the manuscript. Douglas Richman initiated the review, aided in the literature search and data review, supervised the reviewing process, and participated in the writing of the final paper.

Conflicts of interest

There are no conflicts of interest to be reported.

Introduction

HIV infection has been a leading cause of illness and death globally since its recognition 30 years ago. This pandemic most greatly affects sub-Saharan Africa and other resource-limited countries [1]. The increasing availability of anti-retroviral therapy (ART) to over seven million people by the end of 2011 has improved survival and quality of life for many infected with HIV [1, 2].

The increasing availability and use of ART, however, also engenders drug resistance. In North America and Europe, where ART has been widely available, acquired drug resistance rates vary depending on duration of treatment and type of regimen prescribed (non-nucleoside reverse transcriptase inhibitor-based versus boosted protease inhibitor-based) [3–7]. One study from British Columbia, Canada found rates of 27 to 40 percent in patients on ART for more than three years (median time 47.2 months) [3]. Another study indicates that, although acquired drug resistance does increase according to time on ART, population levels of drug resistance decreased from 1999 (50–57%) to 2007 (35–42%) due to the decrease in exposure to regimens containing only nucleosides [7]. Estimates of rates of transmitted drug resistance (TDR) now range from approximately 5–20% [8–10]. In resource-rich countries, laboratory monitoring for drug failure and the development of drug resistance is the standard of care, and multiple anti-retroviral drugs are available for patients with drug-resistant viruses [3, 11]. Without such monitoring, patients may spend months or even years on a failing drug regimen, resulting in accumulating drug resistance and increased rates of morbidity and mortality [12–15].

In resource-limited settings, some data on the emergence of drug resistance have been published; however, these data are fragmentary and presented without standardized criteria for definitions of virological or immunological failure, definitions of drug resistance, durations of follow-up, drug-switching guidelines, methodologies of data analysis, etc. There have also been multiple reviews published on this and related topics, but drug resistance since ART roll-out has not yet been specifically addressed. This review aims to summarize the available information on drug-resistance in adults in resource-limited settings (RLSs) particularly since large-scale ART roll-out. Such information is important to assess efficacy of treatment and to guide future monitoring and treatment needs.

Methods

Search strategy

We systematically reviewed published work in accordance with PRISMA guidelines [16]. The online databases PubMed and Google Scholar were searched for articles available before November 2011, using the terms “drug resistance” or “drug resistant” and “HIV” or “AIDS” or “human immunodeficiency virus” or “acquired immune deficiency syndrome” and “resource limited” or “Africa” or “Asia.” These particular geographic regions were used as search terms based upon HIV/AIDS treatment programs (such as the President’s Emergency Plan for AIDS Relief) known to be in place in these areas. Pertinent conference abstracts were also searched, as were the references from articles found during these searches to find additional relevant articles and abstracts.

Study Selection

This review analyzed published papers and abstracts of studies of adult patients with HIV-1 infections tested for drug-resistance mutations (DRMs) either before the initiation of antiretroviral therapy (ART) in order to evaluate transmitted drug resistance or after initiation of ART in order to evaluate acquired drug resistance. Data from children-specific studies were excluded. A few studies included a limited number of adolescents and these papers were not excluded. Titles and abstracts of papers and meeting abstracts were selected for relevance to drug resistance in resource limited settings. Included studies were conducted in resource-limited countries where HIV patients were treated with highly active antiretroviral therapy (HAART), defined as a three drug regimen consisting of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTIs), or in a few cases, a protease inhibitor (PI). Mutations were analyzed according to the Stanford HIV Drug Resistance (HIVDR) database, the WHO list for surveillance of transmitted HIVDR, the drug resistance interpretation algorithm from the Agence National de Recherche sur le Sida et le Hepatitis (ANRS), or the International AIDS Society-USA recommendations [17–20]. Studies that did not provide information on the overall prevalence of drug resistance mutations (DRMs) or that included common polymorphisms also seen frequently in wild type isolates were excluded [21]. Because of the heterogeneity of the studies, no strict parameters for patient age (other than as described above), sex, CD4 count, viral load, or definition of virological failure were required as long as these characteristics were described and/or standardized within each study. Data were analyzed with consideration for the 2006 UNGASS session where world leaders promised to work toward providing universal access by 2010 and for the large scale roll-out that began in 2007 [22]. Due to this, publications were only included if the data were collected either in 2007 and later, or in 2005 and later if data collection occurred at least one year after rollout. Only studies published in English were included. The majority of possibly pertinent studies excluded either lacked drug resistance prevalence data (major end-point of analysis for this review and therefore necessary for inclusion) or were conducted before the specified study period described above (Figure 1).

Data Analysis

Rates of acquired drug resistance were analyzed according to the number of months patients received ART. Time intervals of 6 to 11 months, 12 to 23 months, 24 to 35 months, and 36 months were compared. Specific drug class mutation rates were also considered, although it should be noted that not all studies provided this information. As a result, the rates for acquired NRTI, NNRTI, and PI mutations were calculated using data from a more limited study population than those available for acquired drug resistance overall.

Resistance in patients identified as treatment naïve was designated as transmitted drug resistance. The prevalence of TDR was analyzed by geographic area: Southern Africa, Middle Africa, Western Africa, Eastern Africa, Asia, and Brazil. United Nations' definitions were used for the African subregions [23]. Insufficient data were available to include Northern Africa, Mexico, and most of South America. TDR was also analyzed by time since ART availability. Studies were assigned to two groups: data collected <5 years after the initiation of ART rollout in the country and data collected ≥5 years after ART availability in

the country. ART availability dates were based upon information given within individual studies. For instance, Aghokeng et al evaluated transmitted HIVDR in both urban and rural settings in Cameroon and used an ART availability date of 2001 in urban sites and 2007 in rural areas [24]. Most other studies used a single year as the start of roll-out. The time point used to measure the number of years from roll-out to data collection was the last year in which data were collected. For example, Price et al collected data between 2006 and 2009, so the data given in that study for South Africa (roll-out 2004) was designated as collected five years post roll-out [25]. The primary summary measures used were prevalence of HIVDR within the HIV-infected population studied and relative risk, which was calculated using these prevalences.

Case numbers were extracted from each individual study independently, then pooled into the groups described below. Collective case numbers, prevalence and incidence for each region, time interval and drug class were computed by summing all eligible cases from applicable studies, without further adjustment. The significance of all categorical comparisons was evaluated with a two-tailed Fisher's exact test.

Results

Of the articles and abstracts searched, seven fulfilled the criteria for the analysis of acquired HIV drug resistance [26–33] and twenty-two for the analysis of transmitted HIV drug resistance [24, 25, 26, 28, 34–51] (Figure 1). Two papers provided data for both analyses [28, 30].

Acquired HIVDR

Rates of acquired HIVDR steadily increased with time on ART (Figure 2, supplementary tables 1 and 2). Resistance was detected in 7.2% of patients on ART for 6–11 months, compared to 11.1% at 12–23 months, 15.0% at 24–35 months, and 20.7% at 36 months. During the 12–23 month period, patients had a relative risk (RR) of drug resistance of 1.6 compared to patients in the 6–11 month stage ($p<0.001$, 95% confidence interval (CI) 1.2–2.0). Patients on ART for 24–35 months were 1.3 times more likely to have drug resistance than those on ART for 12–23 months ($p=0.024$, 95% CI 1.0–1.7), and 2.1 times more likely than those on ART for 6–11 months ($p<0.001$, 95% CI 1.5–2.9). Patients on ART for 36 months were 1.4 times as likely to develop drug resistance as those on ART for 24–35 months ($p=0.110$, 95% CI 0.9–2.0), 1.9 times as likely as those on ART for 12–23 months ($p=0.001$, 95% CI 1.3–2.6), and 2.9 times as likely as those on ART for 6–11 months ($p<0.001$, 95% CI 1.9–4.3).

The distribution of resistance mutations by drug-class reflected the predominance of reverse transcriptase inhibitors (RTIs) included in regimens used in RLSs for prolonged periods (Figure 3, supplementary table 3). For both the 6–11 and 12–23 month time periods, significantly more patients developed NNRTI resistance mutations than NRTI resistance mutations (RR=1.6, 95% CI 1.1–2.4, $p=0.018$ and RR=1.3, 95% CI 1.0–1.6, $p=0.024$ respectively). The prevalence of PI mutations was very low during all follow-up periods while multi-class drug resistance increased steadily over time: 3.7% at 6–11 months, 7.2% at 12–23 months, 15.9% at 24–35 months, and, 21.6% at 36 months. Patients on ART for 36

months had a relative risk of multi-class resistance of 5.9 compared to those on ART for 6–11 months (95% CI 2.9–10.9, $p < 0.0001$), 3.4 compared to those on ART for 12–23 months (95% CI 1.8–5.8, $p < 0.0001$), and 2.8 compared to those on ART for 24–35 months (95% CI 1.4–5.2, $p = 0.003$). Those receiving ART for 24–35 months were 2.1 and 1.2 times as likely to harbor multi-class resistant viruses as those receiving ART for 6–11 and 12–23 months (95% CI 1.3–3.4, $p = 0.002$ and 95% CI 0.8–1.8, $p = 0.3$ respectively). During the 12–23 month time period, patients were 1.7 times as likely to have multi-class resistance as during the 6–11 months time period (95% CI 1.2–2.5, $p = 0.002$).

Transmitted HIVDR

The overall rate of TDR in all resource-limited countries was 6.6% (469/7063). Patients in countries in which ART had been available for ≥ 5 years were much more likely to have transmitted drug-resistance than those living in a country where ART had been available for < 5 years (RR=1.7, 95% CI 1.3–2.2, $p < 0.001$) (Figure 4, supplementary tables 4 and 5). Also, eight of the 18 countries included in this review had transmitted HIVDR rates of 5–15%, which are defined by the WHO as “intermediate levels”: Democratic Republic of Congo (6.1%), Rwanda (7.7%), Cameroon (9.3%), Malawi (9.8%), Togo (10.3%), Uganda (10.8%), Vietnam (8.3%), and Brazil (8.4%). The rates of TDR were below five percent in the other ten countries (supplementary table 6).

The overall reported prevalence of transmitted HIVDR in Africa was 5.7% (233/4069). 2.5% of patients were resistant to NRTIs, 3.1% to NNRTIs, 1.3% to PIs, and 1.1% to more than one drug class. Prevalence varied among subregions: 7.3% (42/574) in Middle Africa, 6.7% (157/2337) in East Africa, 3.0% (21/708) in Southern Africa, and 2.9% (13/450) in West Africa. The relative risk of TDR in Middle Africa compared to Southern Africa ($p < 0.001$, 95% CI 1.4–4.3) or West Africa ($p = 0.002$, 95% CI 0.5–2.2) was 2.5. Similarly, the prevalence of TDR in East Africa was 2.3 times higher than in Southern Africa ($p < 0.001$, 95% CI 1.4–3.7) or in West Africa ($p = 0.001$, 95% CI 1.3–4.3). Regional NRTI, NNRTI, PI, and multi-class resistance rates, respectively, were found to be: 3.8%, 2.8%, 1.7%, and 1.7% in Middle Africa; 2.9%, 3.9%, 1.5%, and 1.5% in East Africa; 0.4%, 1.8%, 0.8%, and 0% in Southern Africa; 2.2%, 1.3%, 0.2%, and 0% in West Africa (supplementary table 7).

In Asia, transmitted HIVDR was identified in 7.6% (160/2094) of patients. 4.3% were resistant to NRTIs, 3.8% to NNRTIs, 0.3% to PIs, and 0.7% to multiple drug classes. Patients in Asia were 1.3 times as likely to harbor a drug-resistant virus as those in Africa ($p = 0.004$, 95% CI 1.1–1.6).

8.4% (76/900) of patients in Brazil had transmitted drug-resistance. NNRTI, NRTI, PI, and multi-class drug resistance rates, respectively, were 3.4%, 4.4%, 2.1%, and 1.4%. Brazilian patients were 1.5 times as likely to be infected with a drug resistant virus as their African counterparts ($p = 0.004$, 95% CI 1.1–1.9), though they had a very similar risk to patients in Asia (RR=1.1, 95% CI 0.8–1.4, $p = 0.46$).

Discussion

The data reviewed here indicate that broad access to antiretroviral therapy in resource-limited settings, in addition to conferring substantial benefits on survival and quality of life, has not surprisingly engendered the emergence of both acquired and transmitted drug resistance. The magnitude of drug resistance, as expected, also increased with duration of treatment in the individual and the duration of access to treatment in the population. The prevalence of transmitted drug resistance varied with geographic region, which is likely attributable to different timelines for access to ART. The relative risk of TDR in both Asia and Brazil is approximately 1.5 times that in Africa, which can be attributed to the fact that ART has been available in Brazil and some Asian countries, like Thailand and Vietnam, since the mid-1990's [36, 49, 50]. Moreover, the early use in these regions included the use of dual nucleoside regimens before the availability of more potent combination triple drug therapies. Dual nucleoside regimens are less likely to suppress virus replication and thus more likely to select for resistance. Within Africa, significantly higher rates of TDR exist in Middle and East Africa than in West or Southern Africa, which in general reflect the timing of the roll-out of ART. In addition to the duration that ART was available, differences in rates of TDR could be attributable to interruption in medication availability (such as medication stock out), suboptimal adherence, regimens prescribed, disease stage at time of treatment initiation, and limited use of viral load monitoring for regimen failure, as these are known risk factors for HIV drug resistance [52–56]. Though there is speculation that certain HIV subtypes may be more prone to the development of resistance than others, this relationship is not well-defined. Because of this and the highly variable distribution of subtypes across Africa, subtype data were not reported in the reviewed publications.

The data reviewed here largely reflect studies of convenience samples rather than results from sampling designed to be representative of the total populations at risk for drug resistance. Furthermore, the available studies included in this review varied widely in their designs, patient populations, inclusion criteria, drug resistance mutation lists, viral load thresholds for genotype sequencing, sequencing protocols, and methodologies of data analysis. In addition, transmitted drug resistance was generally defined as the presence of 1 drug resistance mutation in a previously ART naïve patient, although spontaneous reversion of TDR in the absence of drug selection pressure over time may reduce the estimated prevalence of TDR mutations in patients infected for many years prior to HIV diagnosis [57]. These more stringent criteria exist due to the knowledge that certain mutations, like M184V in reverse transcriptase, decrease the fitness of the virus and will quickly revert back to wild-type in the absence of selection pressure of drug treatment. Accordingly, studies of chronically infected patients included in this review may have underestimated the rates of TDR. Another limitation is that most patients were deemed drug-naïve by self-proclamation. Therefore, some patients with undeclared previous exposure to antiretroviral drugs may be included, which would overestimate the rates of true TDR. It is also important to consider that the year of roll-out in each particular country may not be an accurate measure of time since ART availability. Many urban or more affluent areas had access to ART before roll-out, which could diminish the apparent relationship between rates of TDR and elapsed time since ART availability. Furthermore, most of the data available on genotypic resistance were

collected from patients enrolled in programs where virological monitoring is available. Because the majority of programs in RLSs do not have this expensive option, it is possible that a greater proportion of patients in such programs are continuing on failing drug regimens and harbor drug resistant virus than is stated here.

Even with the limitations in the available data, the results reviewed here have several potential implications for the future of HIV/AIDS treatment programs in resource-limited settings. High rates of acquired drug resistance suggest poor adherence (which can be improved with better counseling and minimizing supply stock-outs), suboptimal regimens, and a lack of monitoring for failure to reduce the continuing use of a failing regimen [58–60]. Drug-resistance monitoring programs in RLSs are limited by cost and laboratory availability [61]. Currently, the WHO recommends universal clinical monitoring for patients receiving ART in RLSs and symptom-directed laboratory monitoring for safety and toxicity. Recommendations for periodic CD4 counts before and throughout treatment also exist, along with suggestions for periodic viral load monitoring where available [62]. Many individual country guidelines, however, recommend only clinical monitoring due to insufficient access to routine laboratory testing [11]. Immunologic and virologic testing have widely accepted clinical benefits, and examination of the cost-effectiveness of these strategies will prove an important part of developing and implementing new monitoring strategies [61]. In the absence of laboratory monitoring, strategies to monitor and improve treatment delivery and patient adherence may help minimize sustained virological failure more than clinical monitoring alone [52, 63]. Another important factor to consider is the limited availability of second line treatment antiretroviral drugs in resource-limited settings. As drug resistance increases, and especially multi-class drug resistance, the need for an expanded pharmaceutical arsenal for effective treatment intensifies. Mtambo et al have also suggested that boosted PI regimens as first-line therapy in RLSs may lead to lower rates of acquired drug resistance while providing equal efficacy to NNRTI-based regimens (27% drug resistance versus 40% drug resistance). In addition, according to DRM profiles, patients on a boosted PI regimen had more options for second line ART than those on NNRTI-based regimens once drug resistance was identified [3]. Analyses of several clinical trials showed similar findings [4]. Currently, PIs are generally only available as second-line treatment if they are available at all, and adding them as an option for first-line treatment, especially for patients with TDR or recently exposed to nevirapine for prevention of prenatal transmission, may be something to consider in the future.

The major aim of ART scale-up programs is to treat as many people as possible, and drug resistance, which compromises treatment efficacy, represents an important factor when considering treatment strategies. Increasing rates of TDR reflect both high rates of acquired drug resistance (especially when unrecognized because of the absence of monitoring for virologic failure) and of inadequate prevention of transmission. The rates of TDR now being observed in many RLSs are an indication in wealthier countries for obtaining a drug resistance test before initiating treatment [64]. Without testing for TDR, first line treatment failure will increase, leading to a further decrease in treatment options due to accumulation of DRMs in individuals with resistant virus [34]. This would not only compromise their second line treatment options, but also compromise treatment in patients newly infected with

the resistant virus. Therefore, greater efforts should be made to expand both effective drug resistance monitoring strategies and treatment options in resource-limited settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Search Strategy

MSM=men who have sex with men.

^aStudies with no drug resistance prevalence data, studies conducted in non-resource limited areas, studies of prevention of mother-to-child transmission, studies involving patients on non-highly active antiretroviral therapy regimens, medication adherence studies, and studies not in English.

Figure 2. Changes in rates of acquired HIVDR to any drug class according duration of treatment
HIVDR=human immunodeficiency virus drug resistance. ART=antiretroviral therapy.

Figure 3. Distribution of acquired HIVDR to individual drug classes according to time on antiretroviral therapy

Drug-class resistance information was not available for all studies. Percentages given were calculated using only the studies which gave drug-class specific information, causing them to be of different proportions than the overall resistance rates presented in figure 2.

HIVDR=human immunodeficiency virus drug resistance. ART=antiretroviral therapy.

NRTI=nucleoside reverse transcriptase inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. PI=protease inhibitor.

Figure 4. Changes in rates of transmitted HIVDR according to time since ART availability
HIVDR=human immunodeficiency virus drug resistance. ART=antiretroviral therapy.
NRTI=nucleoside reverse transcriptase inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. PI=protease inhibitor.