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Temporal Changes in the Epidemiology of Transmission of Drug-Resistant HIV-1 across the World

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Abstract

A substantial number of studies have been performed across the world to determine transmitted drug resistance. Large variations between different parts of the world can be expected because of differences in availability over time of treatment. Time trend analyses are often not possible because of small numbers of included patients. In this review, we present the available data on the transmission of drug-resistant HIV, with a major emphasis on the time trends of drug resistance prevalences. We identified relevant literature by searching in PubMed through September 2009. Studies were grouped, according to the year of data collection, into the following time periods: < 2001, 2001-2003, > 2003. We selected a total of 215 studies, which included 43,170 patients. The following prevalences of transmission of drug-resistant HIV were found, in rank order: North America (12.9%), Europe (10.9%), Latin America (6.3%), Africa (4.7%), and Asia (4.2%). Changes over time in particular drugs classes were found in all parts of the world. Nucleoside reverse transcriptase inhibitor resistance declined over time in North America (p = 0.03), Europe (p < 0.001), and Latin America (p < 0.001). The decline in nucleoside reverse transcriptase inhibitor resistance reflects the improvement of treatment regimens in resource-rich settings. In contrast the resistance prevalence increased in Asia (p = 0.047) and Africa (p < 0.001). This can be explained by the antiretrovirals becoming more available during recent years in these continents. Nonnucleoside reverse transcriptase inhibitor resistance rose over time in North America (p < 0.001), Europe (p < 0.001), Latin America (p < 0.001), and Asia (p = 0.01). This paper gives a complete overview of the epidemiology of resistance of antiretroviral drugs in drug-naive patients worldwide. The time trends that were observed seem to reflect changes in describing prescriptions over time. Changes include the more wide-spread use of antiretroviral drugs in developing countries and the development of therapies from low-active mono-therapies to highly active antiretroviral regimens in the industrialized countries. **(AIDS Rev. 2012;14:17-27)**

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Key words

HIV-1. Drug resistance mutations. Resistance prevalence. Transmitted drug resistance.

Introduction

The use of HAART has substantially improved survival among patients infected with HIV-1. But the success of antiretroviral treatment can be limited by the emergence of HIV drug resistance, which in turn can be transmitted to newly infected individuals. Transmission of drug resistance is associated with an increased risk for virologic failure 12 months after start of treatment[1].

A large number of studies reported on transmitted drug resistance across the world. These studies report a prevalence of transmitted drug resistance that ranges between 0-25%[2-4].

The prevalence is lowest in resource-limited settings[5]. But the prevalence in resource-limited countries may have increased in recent years as access to antiretroviral drugs has been expanding.

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Substantial differences in resistance to particular classes of antiretroviral drugs may exist over time in different parts of the world. For example, the use of nevirapine in Africa to prevent mother-to-child transmission could have increased the prevalence of transmitted resistance to nonnucleoside reverse transcriptase inhibitors (NNRTI) in Africa[6]. Similarly, in resource-rich settings zidovudine was given as monotherapy before 1996, resulting in transmitted nucleoside reverse transcriptase inhibitor (NRTI) drug resistance[7,8]. In recent years, other classes of antiretrovirals have become popular, which could have changed the epidemic of transmission of drug resistance. We conducted a systematic review of the literature to compare temporal changes in the prevalence of transmission of drug-resistant HIV-1 across different continents.

Selection of studies on transmitted drug resistance

PubMed was used to identify studies written in English on the epidemiology of transmission of drug-resistant HIV-1 until September 1, 2009 (key words "HIV" and "resistance" or "HIV" and "transmission"). Primary research studies that investigated the prevalence of HIV drug resistance in antiretroviral-naive HIV-1-infected persons were eligible for inclusion.

Transmitted drug resistance was reported in 215 papers, including 43,170 patients (Table 1).

Most studies came from Europe (82 studies; 25,446 patients), followed by Africa (47; 3,096), North America (36; 8,718), Latin America (26; 3,218), Asia (23; 2,507), and Australia (1; 185). The characteristics of included patients varied between continents. The proportion of risk groups per continent in the included studies followed the regional mode of HIV-1 transmission across the world. For example, in North America and Europe, patients were predominantly infected through men who have sex with men (41 and 47%, respectively), whereas in other continents this did not exceed 20%, as described in literature[9].

Definition of transmission of drug resistance

We compiled transmitted drug resistance as reported in the studies. Resistance to NRTI, NNRTI, and protease inhibitors (PI) was defined as the presence of at least one drug resistance-associated mutation to that particular drug class. Multiclass resistance was defined as the presence of resistance-associated mutations to at least two different classes of antiretroviral drugs. The list used to define transmitted drug resistance was extracted from the studies.

Statistical analysis

Time trends were analyzed by grouping the studies according to the year of data collection: before 2001, 2001-2003, and 2004 or later. We used these cutoffs so that we could include time periods with comparable numbers of patients. Taking different time periods did not result in different trends over time (data not shown). Studies reporting the epidemiology of transmission of resistance over a range of years were grouped according to the average of the years.

Sixteen studies did not report the year of data collection. The average difference between year of data collection and year of publication was four years. We therefore calculated the missing data collection years by subtracting four years from the year of publication. Exclusion of these studies or subtraction of 0, 2, or 6 years from the year of publication did not change the results (data not shown).

Prevalence estimates are presented with 95% confidence intervals calculated according to the Wilson score interval. Poisson regression analysis was used to calculate the time trend analyses for each continent.

Epidemiology of transmission of drug resistance Europe

The studies were predominantly performed in Western Europe (n = 75). A smaller number of studies (n = 7) came from Central Europe and the former Soviet Union. Studies from the former Soviet Union are of particular interest as this part of the world has the strongest growing epidemic worldwide due to an explosive outbreak of HIV-1 infections among intravenous drug users[10-12].

The prevalence of transmission of drug resistance across Europe was 10.9% (95% CI: 10.6-11.3%). Transmission of drug resistance most frequently involved NRTI, with a prevalence of 7.4% (7.1-7.7%). The prevalence of resistance to NNRTI was with a prevalence of 3.4% (3.2-3.6%), slightly higher than the prevalence of 2.9% (2.7-3.2%) found for PI.

Transmission of drug resistance declined over time in Europe. The prevalence was around 11.5% before 2003 and reduced to 7.7% after that year ($p < 0.001$). A closer examination of the classes showed that this decrease was ascribed to the decline in resistance to NRTI (from 8.0 to 4.3%) and PI (from 3.3 to 1.4%) ($p < 0.001$).

Resistance to NNRTI increased from 2.9% to a small peak in 2001-2002 of 4.4%, after which it decreased again to 3.2% (p = 0.004).

Two European studies that reported on the epidemiology of transmitted drug resistance over time confirm our results. First, the pan-European SPREAD program also reported a decrease in the prevalence of transmitted NRTI resistance and an increase in the prevalence of transmitted NNRTI resistance over time (2002-2006). These changes were, however, not statistically significant, which could be ascribed to a smaller sample size in the SPREAD program[13]. The second study confirming the decline in transmitted drug resistance over time was performed in the United Kingdom. This study reported a small increase in NRTI resistance, with some evidence of a leveling off from 1996 to 2003. This British study also reported an increase in transmission of NNRTI resistance[14].

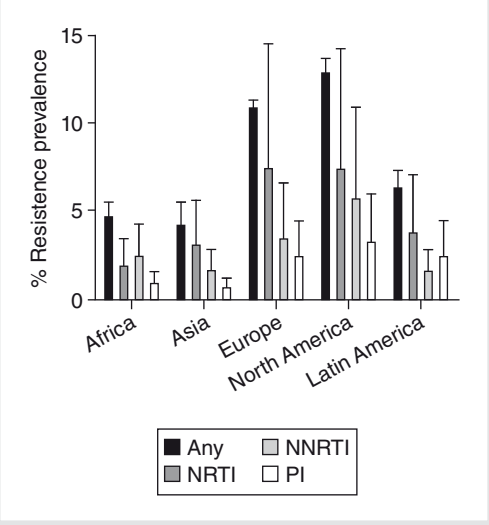

Figure 1. *Prevalence of transmitted drug resistance to any of the drug classes, nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and protease inhibitors in Africa, Asia, Europe, North America, and Latin America. Any: any class of drugs; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor.*

North America

Europe and North America have had the longest access to antiretrovirals across the world. There were, however, several differences between the two continents. In North America, the prevalence of transmission of drug resistance was higher, with a proportion of 12.9% (12.2-13.7%) (Fig. 1). Similar to Europe, transmission of drug resistance was for the largest part ascribed to NRTI; prevalence 7.4% (6.8-8.0%). But transmission of NNRTI resistance in North America was 5.7% (5.2-6.2%), higher than the prevalence of 3.4% found in Europe. Similar to Europe, resistance to PI was also uncommon in North America, with a prevalence of 3.2% (2.8-3.6%) as compared to 2.9% in Europe.

Contrary to Europe, the prevalence of resistance showed an increase over time from 11.6% (10.7-12.7%) in studies performed before 2001 to 14.3% (12.8-16.1%) in studies performed after 2003 (p = 0.003) (Fig. 2). This increase in overall transmitted resistance was ascribed to the increase in NNRTI resistance (from 4.1 to 8.3%; p < 0.001), whereas the NRTI resistance decreased from 8.0 to 6.4% (p = 0.032).

Studies that included longitudinal data confirm the time trends we observed. A study performed in San Francisco showed a decrease in transmitted NRTI resistance from 21% in 1996-1997 to 3.3% in 1998-1999 and a subsequent increase to 6.2% in 2000-2001[8].

The decline in NRTI resistance in resource-rich settings reflects the improvement of treatment regimens. Before 1996, antiretroviral therapy consisted of monotherapy or dual-therapy of NRTI, which lead to the appearance of drug-resistant HIV-1 in many patients[15,16]. After 1996, HAART was introduced, which is virologically more active and is associated with a substantially lower risk of resistance. As a consequence, NRTI resistance was initially high and then decreased in recent years.

The increase of NNRTI resistance in Europe and North America coincides with the more frequent use of this drug class in the developed world in the previous years. NNRTI were approved in 1996 and clinical trials in 1999 indicated that virologic outcomes during treatment with this drug class were better compared with those of PI-based treatment[17].

Latin America

Large Latin American countries, such as Argentina and Brazil, have sponsored a policy of universal access to antiretroviral drugs since the 1990s. Interestingly, transmission of drug resistance was reported in 6.3% (5.5-7.3%) of HIV-1 patients from Latin American studies, suggesting that universal access did not result in high levels of resistance.

Studies from Latin America reported a low prevalence of transmission of drug resistance to the different drug classes: 3.8% (3.2-4.6%) for NRTI, 1.6% (1.2-2.1%) for

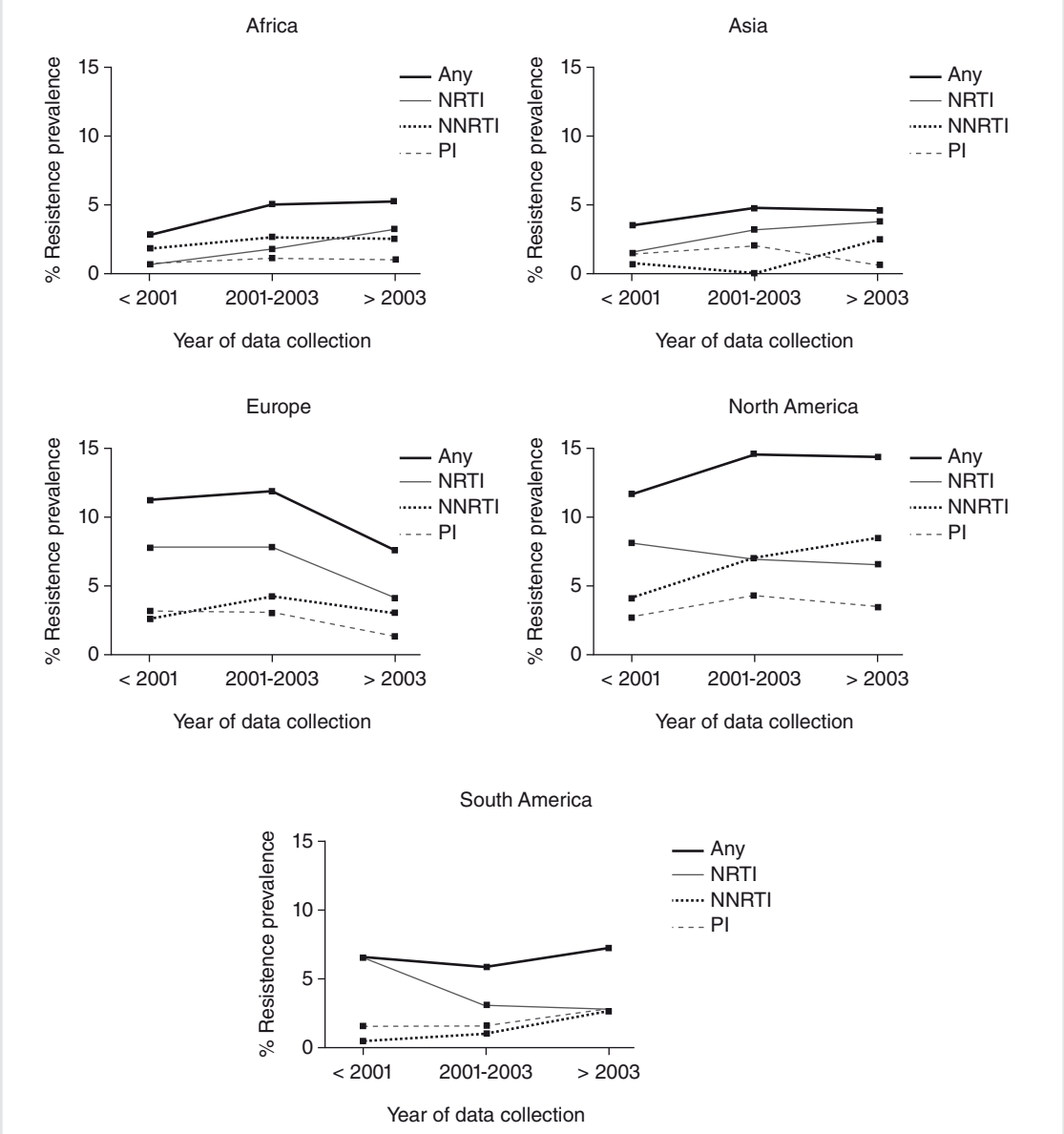

Figure 2. *Prevalence over time of transmitted drug resistance to any of the drug classes, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors in Africa, Asia, Europe, North America, and Latin America. Any: any class of drugs; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor.*

NNRTI, and 2.4% (2.0-2.8%) for PI. The time trends for resistance to particular classes followed the same trend as in Europe and North America. Resistance to NRTI decreased over time (from 6.6 to 2.8%; $p < 0.001$). The prevalence of transmission of NNRTI increased from 0.6 to 2.7% ($p < 0.001$). Resistance to PI increased, but remained limited (from 1.6 to 2.7%; $p = 0.01$).

Transmitted drug resistance to PI was uncommon in all parts of the world (< 3.2%). This may be explained by the high genetic threshold for resistance to boosted PI. Moreover, PI are not used in treatment of all patients as they are frequently reserved for second-line therapy.

Africa

Transmission of drug resistance was variable in Africa and 30 out of 47 studies reported a prevalence < 5%. The combined prevalence of transmission of drug

resistance in studies from Africa was low with a proportion of 4.7% (4.0-5.5%). However, many parts of Africa still do not have access to antiretrovirals. Epidemiological studies on transmitted resistance will not be performed in these areas as resistance is unlikely. Therefore, the transmitted resistance prevalence that we calculated from the available studies performed in Africa is an overestimation of the real prevalence in this continent.

Importantly, transmission of drug-resistant HIV increased over time. The prevalence was 2.8% (1.7-4.5%) before 2001 and almost doubled to 5.3% (4.0-6.9%) after 2003. This increase was, however, not statistically significant ($p = 0.06$). The increase can be explained by the increase in NRTI drug resistance over time from 0.6% before 2001 to 3.0% after 2003 ($p < 0.001$). The prevalence of PI resistance was low (0.9%; 95% CI: 0.6-1.3%) and NNRTI prevalence showed a non-significant increase from 1.7 to 2.5%.

In Africa, different patterns of resistance to particular antiretroviral drug classes were seen than in other parts of the world. Contrary to the Americas and Europe, the prevalence of NRTI resistance increased over time. This increase can be explained by the antiretrovirals becoming more widely available during recent years (e.g. due to the efforts of the Global Fund and PEPFAR, the President's Emergency Plan for AIDS Relief). Due to the increased use of HAART, which includes NRTI as the backbone, resistant mutations have developed, and as a consequence transmitted NRTI resistance in Africa has been rising.

A high proportion of NNRTI resistance was initially observed and is decreasing over time. This high contribution reflects the prophylactic use of a single dose of NNRTI monotherapy for prevention of mother-to-child-transmission[6,18]. Due to the low genetic threshold for resistance to NNRTI, viral resistance could be induced[19]. Currently, the WHO recommends combinations of different antiretroviral drugs, including NRTI, to prevent vertical transmission, instead of using the simplest regimen of single-dose nevirapine[20]. Furthermore, universal access to HAART has been scaled up in developing countries[21,22].

As a consequence, transmitted NRTI resistance has increased and the contribution of NNRTI resistance to the total resistance has decreased.

Asia

We found a lack of data on transmission of drug resistance in Asia. Data from Asia should therefore be interpreted with caution. Only a low number of studies and patients could be extracted from literature. Consequently, time trend analyses showed less significant results.

For example, the overall resistance prevalence of 4.2% (3.4-5.4%) was stable over time ($p = 0.496$). However, NRTI and NNRTI resistance were slightly increasing from 1.3 to 3.5% ($p = 0.047$) and 0.6 to 2.2% ($p = 0.01$), respectively. Transmitted resistance to PI declined over time from 1.3 to 0.4% ($p = 0.02$).

Oceania

Only one study was included from Australia in this review. This study reported a high prevalence of 23.2% (17.7-29.8%). No further analyses were performed with this data.

Discussion

In this review, we examined all literature available on HIV-1 transmitted drug resistance epidemiology. Reviewing all literature on this subject allowed us to calculate the change over time in the prevalence of transmission of drug-resistant HIV-1 for the different drug classes in each continent.

The prevalence of transmitted resistance ranged between 0%[23-26] and 27%[8]. This means that most HIV infections are with a virus that is susceptible to antiretrovirals. There were, however, clear differences across the world. The highest prevalence of transmitted resistance was found in North America (12.9%) and Europe (10.9%), where antiretroviral drugs have been available for prolonged periods of time. Lower proportions of transmitted resistance were found in Latin America (6.3%), Africa (4.7%), and in Asia (4.2%).

Time trends observed in this study may be caused by true differences in temporal changes in treatment regimens between continents, or by other sources of variability. An important factor may be the inclusion of recently or chronically infected patients, a distinction sometimes made in studies performed in resource-rich countries. Resistance in recently infected patients has been reported to be higher than resistance in patients infected > 1 year[27]. This can be explained by several factors. First, the difference partly reflects the variation of resistance prevalence among different HIV risk groups. The majority of the recently infected patients are men who have sex with men (MSM)[28]. Transmitted drug resistance is often much higher in MSM HIV-infected patients compared to the heterosexual risk group because most HIV patients who acquired HIV

through heterosexual contact are more likely to come from regions with limited access to antiretroviral drugs[13,29]. In addition, the lower prevalence of transmitted drug resistance in chronic patients can be explained by the outgrowth of the wild-type or the reversion of the transmitted drug resistance mutations. Remarkably, some resistance viruses remain present in patients, despite the negative effect on replication capacity, due to the appearance of compensatory mutations and the reduced replication capacity of the required intermediate viruses[30]. In this review, the effect of differences between studies in including recently or chronically infected patients on the time trends is probably limited, as most differences in studies were seen between continents and not over time.

Another source of variation in resistance prevalence between studies may be the use of different methods to define drug resistance. The majority of the studies we included have defined resistance either with the IAS USA or the Stanford genotypic resistance interpretation algorithm. However, the use of different algorithms to score resistance may not have a large impact. This is supported by a previous study reporting that scoring resistance using the IAS USA mutation list of 2006[31], or the Stanford HIVdb (version 4.3.0, 2007) or the Shafer list of 2007[32] was associated with comparable levels of transmitted drug resistance in 8,272 genotypic resistance tests of drug-naive patients conducted during 1997-2005[33].

This review is limited by the data that could be extracted from published reports. Convenience sampling (i.e. an over-representation of patients suspected to carry a drug-resistant virus) may have an impact on the prevalence estimates. Although we cannot rule out that convenience sampling occurred, the vast majority of included studies used well-defined sampling strategies to identify relevant patients.

Heterogeneity is another bias that can occur within reviews. Heterogeneity applies to differences in the strategies used to sample patients and in research methodology. We reduced the heterogeneity by taking into account the year of data collection and performing analyses per continent.

The studies that were collected used population sequence analysis. This method fails to detect minor populations of drug-resistant quasispecies[34]. As resistance variants in the absence of drug-selection pressure in the antiretroviral-naive host may be present in minority viral variants, population sequence analysis will underestimate the prevalence of drug-resistant HIV-1.

Despite these shortcomings, this review is the first, to our knowledge, to summarize all the published articles on transmitted drug resistance.

Conclusion

In this paper, we gave an overview of the epidemiology of resistance to antiretroviral drugs in drug-naive patients worldwide. The resistance profiles of the three antiretroviral drug classes seem to be different among continents and reflect changes in prescribing behavior of antiretroviral drugs. Although the prevalence of resistance to antiretroviral drugs decreases, resistance can become a larger problem in third world continents, where antiretroviral drug therapy is becoming more widespread. Continuous global surveillance is needed to monitor the circulating HIV strains and ensure that the development of treatment is adjusted to the evolution of drug resistance.

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Supplementary Data

Supplementary data is available at AIDS Reviews journal online (http://www.aidsreviews.com). This data is provided by the author and published online to benefit the reader. The contents of all supplementary data are the sole responsibility of the authors.

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