Transmission of Drug Resistant HIV and Its Potential Impact on Mortality and Treatment Outcomes in Resource-Limited Settings

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Scale-up of antiretroviral therapy in low- and middle-income countries has been achieved by using a public health approach that involved national standard regimens and clinical monitoring in settings where laboratory infrastructure was not available. This strategy potentially allows for long periods of unrecognized viral failure, during which drug-resistant virus can be transmitted and this could compromise the long-term effectiveness of currently available first-line regimens. In response to this concern, the World Health Organization recommends population-based surveys to detect whether the prevalence of resistance in ART-naive people is reaching alerting levels. Whereas adherence counseling has to be an integral component of any treatment program, it is still unclear which threshold of transmitted drug resistance (TDR) should trigger additional targeted public health actions and which action is the most cost-effective. Mathematical models can contribute to answer these questions. In order to estimate the potential long-term impact of TDR on mortality in people on ART we used the Synthesis transmission model. TDR is predicted to have potentially significant impact on future HIV mortality. It is critical to remain vigilant over transmission of drug-resistant HIV.

Keywords. transmitted drug resistance; mortality; resource-limited settings; HIV; antiretroviral therapy; mathematical model.

Since 2003, the World Health Organization (WHO) has endorsed a public health approach to antiretroviral therapy (ART) aiming to scale up access to ART in resource-limited settings (RLSs). In 2006, the WHO launched a standardized simplified treatment protocol and decentralized service delivery to ensure access to ART to large numbers of human immunodeficiency virus (HIV)-infected people [1]. This public health approach to ART delivery involves using simplified tools, minimizing clinical decision-making, and nationally implementing fixed-dose combinations of first-line regimens. The large-scale production of a limited number of first-line regimens allowed a reduction in prices. These elements resulted in a dramatic expansion in access to ART: 8 million people were on treatment in low- and middle-income countries (LMICs) at the end of 2011. One concern with this simplified approach, often involving switching regimens based on clinical or immunological criteria only, is the potential accumulation of resistant mutations in patients where ART is not fully controlling viral replication, which could lead to extensive transmission of drug-resistant HIV strains, thus potentially compromising the future efficacy of first-line regimens.

To address this concern, WHO has developed population-based survey methods to assess whether significant levels of transmitted drug resistance (TDR) in recently infected populations [2] are emerging in RLSs. The aim of this surveillance is to alert HIV program managers about the level of resistance currently being
transmitted, enabling them to undertake corrective action when possible, and to facilitate comparisons of results across regions and over time.

**PREVALENCE OF RESISTANCE IN ART-NAIVE PEOPLE**

A recent WHO HIV drug resistance report [3], published in July 2012, reported that among 72 WHO surveys of consecutively diagnosed people in areas where TDR should appear first, conducted between 2004 and 2010, 72% were classified as having low resistance (prevalence of resistance <5%) to all drug classes, 28% of them as having moderate resistance (prevalence of resistance between 5%–15%) to 1 or more drug classes, and none as having high resistance (prevalence of resistance >15%). Nevertheless, the percentage of surveys reporting having moderate resistance (prevalence of resistance 5%–15%) increased over time: 18% in the period 2004–2006 versus 32% in 2007–2010. This seems to be due to an increase in the percentages of surveys reporting moderate resistance in Africa: 17.6% (3 out of 17) in 2004–2006 up to 40.7% (11 out of 27) in 2007–2010. Evidence of an increasing trend in non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance was found in Africa (43% in 19 countries), while no significant trend was found in any other region for any drug class. Areas surveyed varied considerably over time, even within the same country, so caution is needed when extrapolating these results beyond the areas surveyed. Globally, 3.1% of the populations surveyed had resistance to any drug class: 1.6% to NNRTIs, 1.3% to nucleoside reverse transcriptase inhibitors (NRTIs), and 0.7% to protease inhibitors (PIs). Among specific mutations, those at position 103 (K103N or S) were the most prevalent (0.8%), followed by those in position 67 (D67N or G), 101 (K101E or P), 181 (Y181C), and 184 (M184V), ranging from 0.3% to 0.4%. In 2009, the prevalence of TDR in these surveys was 4.5% (95% confidence interval [CI], 2.3%–7.2%) in the African region, 2.4% (95% CI, 1.6%–4.8%) in Western Pacific region, and 2.6% (95% CI, 1.1%–6.9%) in a survey from Ukraine. With respect to South East Asia, the most recent survey was conducted in 2007 with an overall HIV drug resistance (HIVDR) prevalence of 1.0% (95% CI, 0.2%–3.8%). A survey from Iran (2006) and Mexico (2004) reported an overall HIVDR prevalence of 7.7% (95% CI, 1.6%–20.9%) and 8.5% (95% CI, 2.4%–20.4%), respectively.

Consistent with WHO surveillance data, a meta-analysis presented in the WHO report (which excludes WHO survey data) found an increased prevalence of resistance among recently and chronically infected ART-naive people up to 6.6% in 2009. Nevertheless, in Africa, where 59 of the 126 surveys included in the reported meta-analysis were conducted, there was no evidence of a statistically significant increase in prevalence of overall resistance and NRTI- or PI-resistant mutations. On the contrary, a statistically significant rise in prevalence of NNRTI mutations was found (from 1% in 2003 [95% CI, 0.3%–2.1%] to 6.4% in 2010 [95% CI, 1.3%–17.5%]). No evidence of change in prevalence of overall or class-specific resistance was found in South East Asia (15 surveys) or Western Pacific region (19 surveys), while a significant increase was found in Latin America and the Caribbean region (33 surveys).

A meta-analysis [4] evaluating trends in resistance in recently and chronically infected ART-naive people (including WHO surveys) in RLSs found a significant increasing trend over time in prevalence of resistance in East Africa (rate of increase of 29% per year; 95% CI, 15%–45%) and Southern Africa (14% per year; 95% CI, 0%–29%), a nonsignificant increasing trend in West and Central Africa (3% per year; 95% CI, 1%–16%) and no change in Latin America. When stratifying by drug class, there was evidence of a statistically significant increase in prevalence of NNRTI-resistant mutations in East (36% per year; 95% CI, 21–52) and Southern Africa (23% per year; 95% CI, 7–42), while this was not the case for any other class of drugs in any other regions. No difference was found in the prevalence of 1 or more resistant mutations between chronic and recent infections.

In high-income countries, where ART has been available since the late 1980s, studies on TDR reported some striking differences, with prevalence of resistance in ART-naive people ranging from 5% (in some parts of Europe) to 25% (in some US cities). In addition, different trends have been observed: a significant decreasing trend followed by a plateau was observed in Europe [5] and in Australia [6], while TDR seemed to have increased over time in the United States [5] and Japan [7].

A multicentre prospective cohort study of almost 2500 ART-naive people recruited between 2007 and 2009 in Kenya, Nigeria, South Africa, Uganda, Zambia, and Zimbabwe [8] found that the highest prevalence of TDR was in Uganda (11.6% compared to 3.5% in all the other sites together) and that this high level of TDR was significantly associated with time since ART rollout. Other smaller studies reported increasing levels of TDR in East, Central, and Southern Africa; India; and Peru [9–11].

**ROLE OF MATHEMATICAL MODELS IN UNDERSTANDING AND PREDICTING TDR IN RLSs**

Although increasing trends in levels of TDR have been observed in RLSs, it is not clear whether these trends will continue to increase or whether they have already reached a plateau. In contrast to resource-rich settings where before the late 1990s patients were initiating mono- and dual-therapy (which incompletely suppressed HIV replication and selected for drug-resistant virus), in RLS populations, potent fixed-dose combination regimens have been initiated. Such regimens are more likely to suppress HIV-RNA, and are associated with higher adherence
Conversely, in most RLSs, viral load monitoring to detect viral failure is not routinely performed, HIVDR testing is not affordable, and availability of second-line regimens is limited. In these cases, people are monitored clinically or with CD4 lymphocyte counts and are likely to stay on virologically failing regimens for longer periods of time, with a consequent higher chance of transmitting resistant virus.

It is quite challenging to predict whether rates of TDR will continue to increase over time, because there is still limited evidence regarding the relative rate of transmission of resistant strains compared to wild-type strains, and limited evidence on the persistence of these strains in majority and minority variants when a person is infected with a resistant virus. In addition, most of the evidence comes from high-income settings where the predominant subtype is B, so it is not certain that this knowledge is relevant for RLSs, where the predominant subtypes are non-B.

Mathematical models can provide some useful insights, identifying the most influential parameters in determining an increase in TDR. They have the potential to be particularly valuable in exploring what would be the most effective and cost-effective policy to undertake if TDR reaches alerting levels.

Mathematical Models: TDR and ART Coverage
Since the beginning of ART roll-out, mathematical models have been used to estimate transmission of resistant virus and most of them found [13–16] that the impact of ART on HIV incidence is dependent on ART coverage [13, 17] and that prevalence of ART resistance (not only transmitted) would increase as ART availability increases [13, 15].

One of the first models that explored the impact of expanding treatment access on TDR in RLSs was published by Blower et al [13]. They predicted that providing ART to 10%–50% of an HIV-infected population was likely to result in 5.9% (inter-quartile range, 2.5%–11.7%) of new infections being resistant in 10 years from baseline [13]. Predictors of an increase in prevalence of TDR were high rate of ART coverage, high relative transmissibility of the resistant strains, increase in risky sexual behavior (from no increase to 2-fold), rate of emergence of acquired resistance (from 20% to 70% of treated cases developing acquired resistance per year), and ineffective treatment regimens. Given the initial plan to roll out ART in Africa to 3 million individuals [18] (corresponding to 5%–10% of the HIV-infected population), Blower et al [16] estimated that, even after 10 years, the proportion of new infections with TDR would have been below 5%. Following the WHO plan to implement surveillance of TDR, Vardavas et al [14] evaluated whether the threshold of 5% being infected with TDR would have been reached in Botswana by 2009. They concluded that this would have been unlikely, but that if the rate of acquired resistance was very high and the resistant strains were as fit as wild-type strains, TDR could be as high as 15%. Recently, Wagner et al [19] investigated the impact of universal access to treatment compared with a universal “test and treat” strategy (annual HIV testing of the entire population and immediate ART regardless of CD4 lymphocyte cell count) on HIV incidence and TDR. They predicted that the incidence of TDR would remain below 0.1% and that widespread access to treatment could, in some cases, even reduce transmission due to the increased selection of drug-resistant strains in people on ART, which were assumed 50% less transmissible than wild-type strains.

LEVELS OF TDR AT WHICH PUBLIC HEALTH ACTION IS INDICATED
A key question is to determine the threshold of TDR prevalence above which it would be appropriate to act on the findings by making appropriate public health interventions, and what would be the most cost-effective action. At the moment, the options appear limited. In high-income settings, the standard approach is to conduct genotypic resistance testing in all individuals initiating ART and to choose a drug regimen which is predicted to be active. Unfortunately, access to resistance testing is currently very limited in most RLSs. An alternative in response to high levels of TDR is the introduction of virological monitoring, which, by minimizing the time spent on a failing regimen with resistant virus, has the potential to limit the number of transmissions with resistant virus. Another option, which has been discussed, is changing the first-line regimen at a national level, from an NNRTI-based regimen to a boosted protease inhibitor (bPI)–based regimen, which is already available in many countries as a second-line regimen. However, because bPI regimens are more expensive than NNRTIs, it is unclear whether this is a more cost-effective strategy than introducing individual-level baseline resistance testing or virological monitoring.

Mathematical Models: Impact of the Introduction of Virological Monitoring
Some models evaluated the impact of introducing virological monitoring compared with clinical monitoring in terms of TDR in RLSs [15, 20, 21]. Baggaley et al [15] found that an increase in ART coverage in people with AIDS or pre-AIDS in an RLS such as Malawi was associated with a rise in the emergence and spread of drug resistance, and that only the withdrawal of ART (it was assumed that only first-line of ART was available) soon after viral rebound could have a substantial impact on drug-resistance emergence, because most of the transmissions of resistant HIV strains were predicted to occur before immunologic treatment failure. Others looked at the impact of different frequencies of virological monitoring on the acquisition and transmission of resistant mutations in South East Asia (Thailand) [20]. They predicted that after 10 years of universal

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ART, in the absence of virological monitoring of treatment and access to second-line regimen, resistance would be detected in 24% of new infections (as minority or majority variants) and in 17% of individuals eligible for ART. The authors identified that the main predictors of an increase in prevalence of TDR were longer average time for resistant strains to revert from majority to minority variants, and high relative fitness of drug-resistant strains. They predicted that if virological monitoring was carried out on a yearly basis for people on ART, and if people were switched to second-line regimen a week after virological failure, prevalence of TDR among ART-naive asymptomatic people would drop below 5%, an 80% relative reduction [20].

A stochastic model exploring the impact on TDR of timing of implementation of viral load in RLSs with generalized epidemics [21] and limited access to treatment (44% of those in need using a threshold of CD4 <200 by 2010) found that the proportion of new infections with TDR by 2020 would be 12.4% if only clinical monitoring was used, and that this prevalence could be reduced to 5.4% or 6.1% if viral load monitoring was introduced in 2010 and 2015, respectively.

Mathematical Models: Impact of Changing the National First-Line Regimen to a Protease Inhibitor–Based Regimen

Walensky et al [22] investigated whether changing first-line regimen to a bPI-based regimen followed by an NNRTI-based second-line regimen, compared with first-line NNRTI-based regimen followed by second-line PI-regimen or absence of ART was cost-effective in Cote d’Ivoire. The authors found that using a PI-based regimen as first-line was not favorable (smaller health benefit and higher cost-effectiveness ratio), regardless of the levels of NNRTI resistance prevalence (up to 76%) and of the efficacy of an NNRTI regimen in suppressing viral replications in people with resistance to NNRTI.

Following the results of the Optimal Combination Therapy After Nevirapine Exposure (OCTANE) trial, which demonstrated that lopinavir/ritonavir (LPV/r) first-line treatment was superior to nevirapine (NVP)–based regimens in women previously exposed to sdNVP, Ciaranello et al [23] assessed whether it was cost-effective to replace the first-line of treatment with LPV/r based regimen in women previously exposed to sdNVP, despite being 4–12 times more expensive than NVP-based regimens. They found that first-line NVP increases life expectancy to 15.2 years, compared with 1.6 years if ART is not available, with an incremental cost-effectiveness ratio (ICER) of $810 per year of life saved (YLS), and that first-line LPV/r increases life expectancy further, up to 16.3 years, with an ICER of $1520/ YLS compared with first-line NVP. This is considered “very cost-effective” (ie, the ICER is below the GDP per capita) for a country like South Africa for whom GDP was $5700 in 2008, and it remains such unless the 24-week efficacy (HIV RNA viral load <400) of the second-line NVP-based regimen is below 13% (below published data) or the efficacy of the second-line LPV-based regimen is above 87%. It becomes less cost-effective if the prevalence of NNRTI resistance decreases or if the time between receiving sdNVP and starting treatment increases. In addition, they found that in women previously exposed to sdNVP, a genotypic resistance test at ART initiation to determine whether to start an NVP-based or LPV/r-based regimen is a cost-effective strategy compared with changing the first-line treatment to LPV/r for all women.

The option that is most cost-effective is likely to be country and/or region dependent, mainly driven by the level of TDR, the cost-effectiveness threshold, and costs of the different options. Among women receiving antiretroviral drugs for prevention of mother-to-child transmission (PMTCT), it is likely that the threshold at which it is opportune to intervene by changing PMTCT regimen is much lower because if women do not have an optimal virological response, they are more likely to transmit HIV (in this case, likely to be a resistant strain) to their babies.

Response to ART in People With Resistant Mutations

Presence of transmitted resistant mutations can reduce the virological response to ART [24], although limited data are available for RLSs. The largest study available is a cohort from 6 countries in sub-Saharan Africa, which recruited over 2500 patients between 2007 and 2009 [25]. They observed that 5% had pretreatment drug resistance to at least 1 drug in the first-line regimen. Of these, 75% were on treatment and virologically suppressed at 12 months compared to 91% among those without pretreatment resistance. This group was estimated to have a 2-fold increase in risk of virological failure (HIV RNA >400 copies) and acquired drug resistance compared to those without resistance at baseline.

IMPACT OF TDR ON DEATH RATES

The poor virologic response in people initiating ART with a non–fully active regimen could lead to increased death rates and an increase in new infections with resistant strains. However, due to the fact that the impact of being infected with a resistant strain on these outcomes is indirect (via a variably reduced virologic response to ART), it is difficult to imagine the likely level of such risk. Certainly, if we assume that many of the newer drugs currently in use or in development in resource-rich settings are made available in RLSs in the future, this will mitigate the risk of a major impact of TDR. If, though, we assume that the range of drugs available in the future will remain limited to those now in use, it is informative to try to quantify the impact on mortality over a medium to long time scale. To this end, we used an existing validated stochastic simulation model of HIV transmission, progression, and the effect of ART, which incorporates transmission of TDR and impact on virologic response of specific resistance mutations, in order to
study long-term outcomes for epidemics characterized by various levels of TDR (see Brief Supplementary Methods). In particular, we sampled from distributions of model parameters reflecting uncertainty and variability between settings in order to generate a series of epidemic scenarios up to an arbitrary baseline time point of 2015. Our model incorporates the loss of mutations in the process of transmission or over time in the new host, which rate has been estimated in observational data from UK (personal communication by H Castro, MSc, November 2012), as well as the uncertainty over these. We then compared outcomes, over 45 years from baseline, according to whether there was (1) no change in the ability of resistant virus to be transmitted, or (2) a theoretical, counterfactual scenario in which transmission of drug resistance was not possible from baseline onwards.

Table 1 shows the characteristics of the epidemics generated at baseline. Table 2 shows the median (90% uncertainty range) percent of new infections with TDR up to 45 years across the simulated epidemics according to the level of TDR at baseline. The table shows a plateau effect for each of the 3 scenarios from 15 years and beyond, which likely relates to the loss of mutations at the time of transmission and over time in the new host. It also shows that epidemics that have higher levels of TDR at baseline tend to continue to have higher levels of TDR throughout, because if conditions allowed for high TDR prevalence at baseline, these conditions will also continue to lead to higher TDR levels over the years after baseline. Table 3 shows the percent reduction in death rate (1 – hazard ratio × 100%) among people on ART, comparing the scenario with no change in the ability of resistant virus to be transmitted with a theoretical scenario where resistance transmission is not occurring, again according to the level of TDR at baseline and the time period of follow-up. Where TDR is low, the impact of its elimination is relatively small, while if it is large, then the impact becomes substantial with increasing time of follow-up, at over 10%.

These are the first estimates to our knowledge of the impact of TDR on mortality at the population level. Clearly, predictions based on mathematical modeling depend on the assumptions made (see “Supplementary Methods,” “HIV Synthesis model details and parameter values,” for more details). In addition, the longer the predictions period is, the higher the uncertainty regarding them is. Nevertheless, these results do help us get into perspective how the impact of drug resistance and its transmission could play out in the longer term. One further important caveat is that our findings relate to adult mortality. For children, the impact of TDR on mortality could well be of greater magnitude, as the pathway from resistance to virologic failure, immunologic failure, clinical failure, and death seems much faster than in adults.

In conclusion, until such time as the goal of zero new HIV infections is reached, there will be a need to start as many people in need on ART as soon as possible. Increased transmission of drug resistance poses a threat to the future efficacy of those drugs. WHO has in place a strategy for supporting monitoring of emerging drug resistance and transmission and of early warning indicators to assess clinics and programmatic factors favoring resistance emergence. The most cost-effective public health response that should be triggered by the identification of high levels of TDR is the subject of ongoing modeling-based research. This line of work will be relevant because

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (90% range)</th>
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<tbody>
<tr>
<td>Number alive in entire population</td>
<td>29 330 (25 254–32 102)</td>
</tr>
<tr>
<td>Number with HIV</td>
<td>3879 (1062–7110)</td>
</tr>
<tr>
<td>HIV prevalence (%)</td>
<td>13 (3–27)</td>
</tr>
<tr>
<td>% of new infections with TDR (any class)</td>
<td>29 (6–58)</td>
</tr>
<tr>
<td>% of new infections with NNRTI resistance</td>
<td>23 (3–26)</td>
</tr>
<tr>
<td>% of HIV-positive people diagnosed</td>
<td>52 (31–88)</td>
</tr>
<tr>
<td>% of diagnosed on ART</td>
<td>32 (13–55)</td>
</tr>
</tbody>
</table>

Table 2. Predicted Trend in TDR (Median % with NNRTI TDR) According to Level at Baseline (in 2015) and Years from Baseline

<table>
<thead>
<tr>
<th>Years from baseline</th>
<th>Prevalence of NNRTI TDR at baseline</th>
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<tbody>
<tr>
<td>&lt;10%</td>
<td>10%–20%</td>
</tr>
<tr>
<td>Baseline</td>
<td>7%</td>
</tr>
<tr>
<td>15</td>
<td>14%</td>
</tr>
<tr>
<td>30</td>
<td>15%</td>
</tr>
<tr>
<td>45</td>
<td>17%</td>
</tr>
</tbody>
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Table 3. Predicted Impact of TDR on Mortality

<table>
<thead>
<tr>
<th>Years from baseline</th>
<th>Prevalence of NNRTI TDR at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–15</td>
<td>1 (1–2)</td>
</tr>
<tr>
<td>15–30</td>
<td>4 (3–5)</td>
</tr>
<tr>
<td>30–45</td>
<td>5 (3–8)</td>
</tr>
</tbody>
</table>

Estimated percent reduction in death rate (95% confidence interval) in people on ART if new TDR prevented, based on a modeling comparison of predicted long-term mortality after baseline between the predicted outcome and that under a counterfactual scenario where new TDR is prevented. Each estimate is based on fitting of a generalized linear model of log death rate on a binary variable indicating whether TDR is eliminated or not, fitted on the data set of 5000 epidemic scenarios.

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models have already been established to provide a useful means to be able to clarify and quantify the potential future impact of TDR. The modeling results we have presented here suggest that the long-term impact of moderate to high levels of TDR on mortality could be substantial, and thus it is critical to remain vigilant about monitoring transmission of drug-resistant HIV.

Supplementary Data

Supplementary materials are available at The Journal of Infectious Diseases online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Errors should be addressed to the author.

Notes

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