HIV/AIDS Programme

WHO HIV DRUG RESISTANCE REPORT 2012

World Health Organization

HIV/AIDS Programme

WHO HIV DRUG RESISTANCE REPORT 2012

World Health Organization

WHO Library Cataloguing-in-Publication Data

The HIV drug resistance report - 2012.

1.Anti-HIV agents – therapeutic use. 2.Drug resistance, Viral – drug effects. 3.HIV infections – epidemiology. 4.HIV infections – drug therapy 5.Population surveillance. 6.Sentinel surveillance. 7.Developing countries. 8.World health - statistics. I.World Health Organization.

ISBN 978 92 4 150393 8 (NLM classification: QV 268.5)

Design & layout: L'IV Com, Villars-sous-Yens, Switzerland

Printed in the USA

TABLE OF CONTENTS

ACRONYMS

3TC	lamivudine
ABC	abacavir
ART	antiretroviral therapy
AZT	zidovudine
bPI	boosted protease inhibitors
CRF	circulating recombinant form
DNA	deoxyribonucleic acid
d4T	stavudine
ddI	didanosine
EFV	efavirenz
ETR	etravirine
FTC	emtricitabine
HIV	human immunodeficiency virus
NNRTI	non-nucleoside reverse-transcriptase inhibitor
NRTI	nucleoside reverse-transcriptase inhibitor
NVP	nevirapine
PCR	polymerase chain reaction
PI	protease inhibitors
PMTCT	prevention of mother-to-child transmission of HIV
PR	protease
RNA	ribonucleic acid
RPV	rilpivirine
RTI	reverse transcriptase inhibitor
RT-PCR	reverse-transcriptase polymerase chain reaction
SDRM	surveillance drug resistance mutation
TAM	thymidine analogue mutation
TDF	tenofovir

ACKNOWLEDGEMENTS

This report was produced by Silvia Bertagnolio (HIV Department, World Health Organization), Michael R. Jordan (HIV Department, World Health Organization), Jhoney Barcarolo (consultant) and Neil Parkin (consultant, Data First Consulting, Inc). Silvia Bertagnolio developed the analysis plan and provided overall coordination. All members of the core team contributed to the review, analysis and quality assurance of the data, writing and editing of the report and the preparation of figures and tables. Martina Penazzato assisted with research and review, and Adil Bahalim provided data management support. We thank Jos Perriens, coordinator of Technologies and Commodities Team, for reviewing drafts of this manuscript at various stages.

This work would not have been possible without the collaboration of national HIV programme managers and staff who supplied the surveillance data that underpins this report. Development and publication of this report were also supported by the generous financial contribution of the Bill and Melinda Gates Foundation. We are sincerely grateful to Christine Rousseau and Chris Duncombe for their continued support. We are indebted to Diane Bennett for her significant contribution to the development of the WHO HIV drug resistance surveillance and monitoring strategy, and to Karen Kelley, particularly for her important work on improving guidance and tools for early warning indicators.

We would also like to thank Annemarie Wensing, Elliot Raizes, Scott Hammer, Raph Hamers, Mark Wainberg (current chair of the HIVResNet), for reviewing the report and providing valuable comments on initial drafts; John Gregson, Daniel Davis, Andrew Phillips, and Valentina Cambiano for the statistical analysis; Daniel Davis and Ravi Gupta for their contribution on the systematic review of acquired and transmitted drug resistance; Andrea De Luca, Anna Hearps, Mark Wainberg, Scott Hammer, and Wataru Sugiura for contributing to the section of resistance in high-income countries; members of HIVResNet for their valuable inputs to develop the drug resistance survey methods, in particular to Mark Myatt and Don Sutherland; Annemarie Wensing and Anne-Mieke Vandamme, Jonathan Schapiro, Rami Kantor and Robert Shafer for their contribution to the interpretation of data from WHO surveys; and Tommy Liu, Robert Shafer, Anne-Mieke Vandamme, and Tulio de Oliveira for assistance with sequence analysis and drug resistance interpretations.

We sincerely thank Tobias F. Rinke de Wit, Raph Hamers and Kim Sigaloff for making available data from the PharmAccess African Studies to Evaluate Resistance (PASER), and the United States Centers for Disease Control and Prevention (CDC) for its contribution to the development and implementation of the HIV drug resistance strategy.

The laboratory members of the WHO HIVDR Network have been essential to the production of high-quality drug resistance surveillance data. The authors would like to thank Chunfu Yang (International Laboratory Branch, CDC/GAP, Atlanta), Martine Peeters (Laboratoire Rétrovirus IRD, Montpellier), and Paul Sandstrom (PHAC, Ottawa) for their support in genotyping specimens for the WHO HIV drug resistance surveys. In addition, the authors would like to thank all the other members of the network for producing high-quality surveillance data:

- Ramatou Toure and Christiane Adje (RETRO CI, Abidjan, Cote d'Ivoire)
- Almaz Abebe and Libsework Muluneh (HIV and Other Viral Disease Research, EHNRI, Addis Ababa, Ethiopia)
- Avelin Aghokeng (IMPM-IRD/CREMER, Yaounde, Cameroon)
- Clement Zeh (KEMRI/CDC HIV Research Laboratory, Kisumu, Kenya)
- Coumba Toure Kane and Souleymane Mboup (Bacteriology-Virology UTH A Le Dantec , Dakar, Senegal)
- Mariza Morgado and Jose Carlos Couto Fernandez (Laboratory of AIDS and Molecular Immunology, Oswaldo Cruz Foundation - FIOCRUZ, Rio de Janeiro, Brazil)
- Luke Hanna (Department of Clinical Research Tuberculosis Research Centre (ICMR), Chennai, India)
- Srikanth Tripathy and Ramesh Paranjape (National AIDS Research Institute, Indian Council of Medical Research, Pune, India)
- Siriphan Saeng-aroon (National Institute of Health, Department of Medical Sciences, Nonthaburi, Thailand)
- Ruengpung Sutthent (Dept Microbiology, Siriraj Hospital, Bangkok, Thailand)
- Shao Yiming (Division of Research on Virology and Immunology (DRVI), NCAIDS, Chinese Center for Disease Control and Prevention, Beijing, China)
- Ping Zhong (Shanghai Municipal Center for Disease Control and Prevention, Shanghai, China)

- Hong Shang (Key Laboratory of Immunology of AIDS, Ministry of Health, Shenyang, China)
- Gillian Hunt, Johanna Ledwaba, and Lynn Morris (AIDS VIRUS RESEARCH UNIT, National Institute for Communicable Diseases, Johannesburg, South Africa)
- Chris Parry and Pontiano Kaleebu (MRC/UVRI Basic Sciences Laboratory, Entebbe, Uganda)
- Georges Dos Santos (Service de Virologie Immunologie Centre Hospitalier et Universitaire de Fort-de-France, Fort-de-France, Martinique)
- Anna Hearps, Vicki Edouard, Adele Lee-Wriede and Suzanne Crowe (Clinical Research Laboratory, Burnet Institute for Medical Research and Public Health, Melbourne, Australia)
- Wendy Stevens (CLS Genotyping Laboratory, Johannesburg General Hospital, Johannesburg, South Africa)
- Yasuhiro Yamamura (AIDS Research Program-Immunology Reference Laboratory, Ponce, Puerto Rico)
- Leon McNally and Philip Cunningham (NSW State Reference Laboratory for HIV and Molecular Diagnostic Medicine, Sydney, Australia)
- James Brooks (National Laboratory for HIV Genetics, PHAC, Ottawa, Canada)
- Patricia Pinson and Herve Fleury (Laboratoire de Virologie, CHU, Bordeaux, France)
- Rob Schuurman (Department Of Virology, University Medical Center Utrecht, Utrecht, Netherlands)
- Carmen Mendoza and Vincente Soriano (Infectious Diseases Department, Hospital Carlos III, Madrid, Spain)
- Pat Cane and Deenan Pillay (Health Protection Agency, London, United Kingdom)

We would also like to thank staff from WHO offices, including Emil Asamoah-Odei, Richard Banda, Fatim Cham, Christopher Dye, Guy-Michel Gershy-Damet, Noreen Jack, Patrick Kombate-Noudjo, Paul Assimawe Pana, Brian Pazvakavambwa, Giovanni Ravasi, Nirina Razakasoa, Padmini Srikantiah and Dongbao Yu.

EXECUTIVE SUMMARY

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. Although it can be minimized, some degree of 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. Therefore, WHO initiated global surveillance of HIV drug resistance in 2004 in order to adequately monitor the emergence of HIV drug resistance as countries scaled up access to antiretroviral therapy.

This report reviews data on HIV drug resistance in low- and middle-income countries between 2003 and 2010 and three main conclusions stand out. First, with the expansion of treatment achieved over the last eight years, there are signals of increasing prevalence of transmitted HIV drug resistance, particularly to non-nucleoside reverse transcriptase inhibitors (NNRTI), among recently infected populations in the areas surveyed. However, though increasing, transmitted HIV drug resistance has not occurred at the high levels some had predicted as a consequence of the rapid scale-up of antiretroviral therapy.

Second, with respect to acquired drug resistance, WHO surveys indicate that, if people are switched to second-line regimens soon after virological failure, standard second-line treatment combinations are likely to be effective for the majority of patients failing first-line therapy.

Third, drug resistance surveillance provides important information on the effectiveness of ART programmes and services. Monitoring of ART programme functioning through WHO HIV drug resistance early warning indicators in 50 countries highlight the existence of important gaps in service delivery and programme performance, particularly with respect to procurement and supply systems, adherence and clinic retention.

Although HIV drug resistance data from low- and middle-income countries are increasingly available, lack of surveillance data over time substantially limits the ability to assess trends in these countries. As ART coverage continues to grow, national programmes should perform routine surveillance of transmitted and acquired HIV drug resistance to optimize programme planning and management and to inform antiretroviral therapy policy.

Drug resistance explained

HIV drug resistance can be categorized as:

- transmitted resistance, which occurs when previously uninfected individuals are infected with a drug-resistant virus; and
- acquired resistance, which occurs when resistance mutations emerge because of drug-selective pressure in individuals receiving antiretroviral therapy.

It is essential to implement routine surveillance of transmitted and acquired HIV drug resistance. WHO transmitted drug resistance surveys alert programme managers to the existence of drug-resistant HIV among recently infected populations in specific geographical areas. WHO surveys of acquired HIV drug resistance estimate prevalence and patterns of resistance at treatment initiation, the proportion of people achieving successful virological suppression at 12 months at sentinel sites and describe drug resistance in populations experiencing treatment failure.[1]

Monitoring HIV drug resistance is critical for optimal programme 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.

Drug resistance in high-income countries

Data suggest that 10–17% of ARV-naïve individuals treated in Australia, Japan, the United States of America and Europe are infected with virus resistant to at least one antiretroviral drug. These levels of drug resistance occurred early after antiretroviral therapy was introduced in many high-income countries in the late 1990s but have since plateaued. The proportion of people achieving treatment success (viral load suppression) has increased over time, thus reducing the emergence of acquired drug resistance and its subsequent transmission.

1 WHO surveys to assess transmitted and acquired drug resistance are not intended to be nationally representative. Additionally, areas surveyed may vary considerably among countries and across time, so generalizations may not be appropriate or applicable.

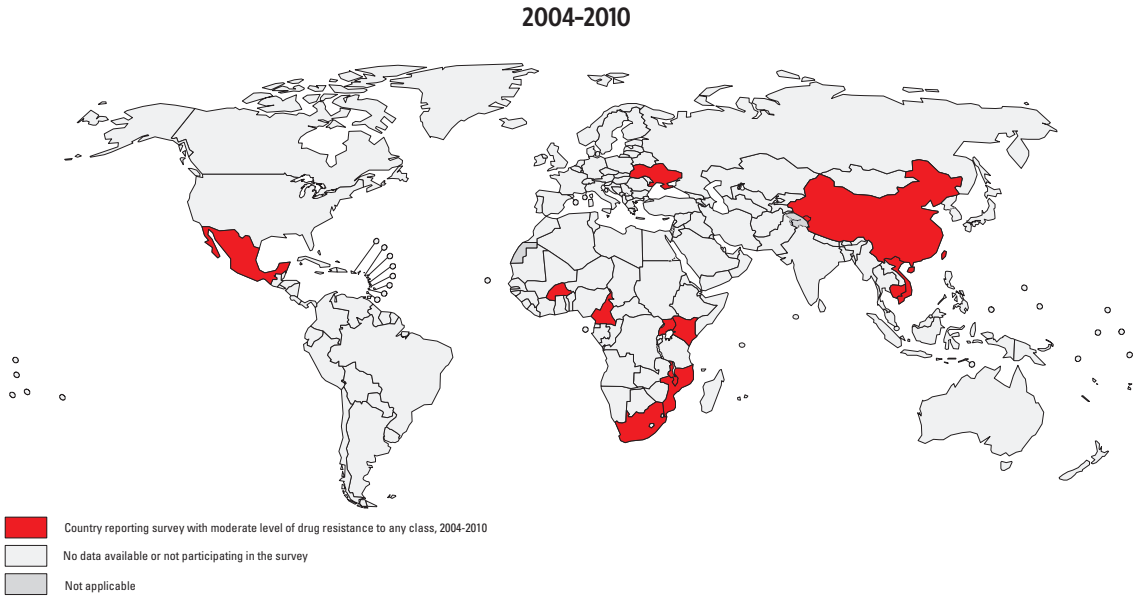
Transmitted drug resistance in low- and middle-income countries

A systematic literature review suggests that the prevalence of drug resistance in select low- and middle-income countries increased between 2003 and 2010, reaching a peak of 6.6% in 2009 (95% confidence interval 5.1%-8.3%).

Pooled analysis of data from WHO surveys, which target people who have been recently infected, indicates that there appears to be increasing levels of resistance to NNRTI, particularly in the areas surveyed in Africa, where the prevalence of NNRTI resistance reached 3.4% (95% CI 1.8%–5.2%) in 2009. There is no clear evidence of increasing HIV drug resistance levels for other drug classes.

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 (Figure 1). The proportion of surveyed areas reporting moderate levels of transmitted drug resistance increased from 18% in 2004-2006 to 32% in 2007-2010 (Table 1). These findings deserve particular attention. If confirmed and documented in multiple areas of the same country, immediate investigation is recommended to understand their determinants and policy implications.

Figure 1 Geographical distribution of WHO surveys with moderate (between 5% and 15%) levels of drug resistance to any drug class[a]



a Areas surveyed varied considerably among countries and over time.

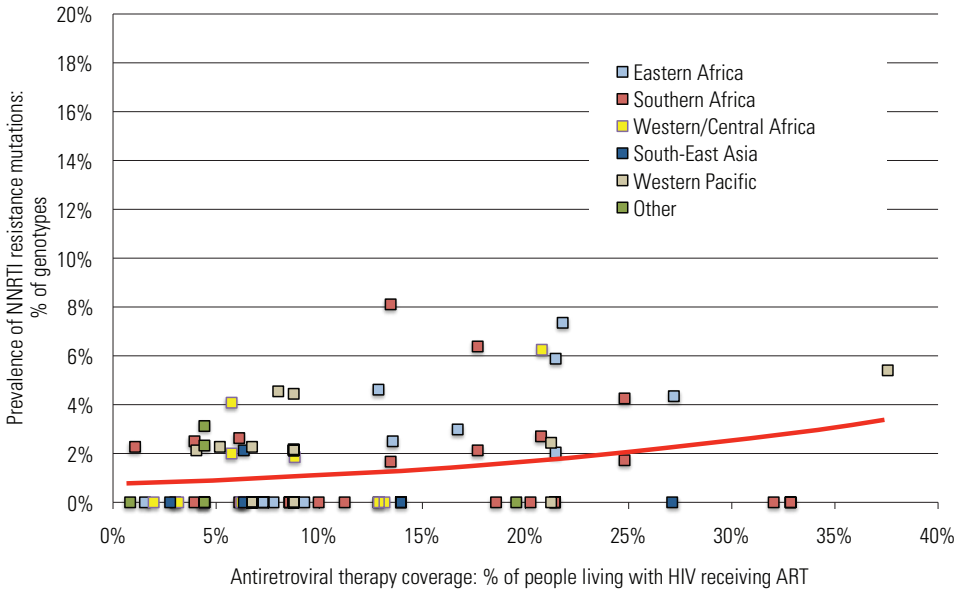
Table 1 Frequency of WHO surveys reporting moderate prevalence of transmitted HIV drug resistance, by period (before or after 2007)[a]

		Number (%) of surveys with moderate (5–15%) prevalence			
Year	Total surveys	Any drug class	NNRTI	NRTI	PI
2004-2006	22	4 (18%)	1 (5%)	3 (14%)	0 (0%)
2007-2010	50	16 (32%)	11 (22%)	7 (14%)	2 (4%)

a Mid-point period.

Available data – summarized in Figure 2 – suggest that there is an association between higher levels of coverage of antiretroviral therapy and an increased prevalence of transmitted drug resistance to NNRTI, such as nevirapine or efavirenz. However, compared with the dramatic increase of treatment coverage, the observed rise in HIV drug resistance was modest. This implies that the expansion of antiretroviral therapy did not trigger unexpected increases in transmitted drug resistance in the areas surveyed.

Figure 2 Relationship between transmitted resistance to NNRTI drugs and antiretroviral therapy coverage



P-value adjusted for region= 0.039; Odds-ratio per 10% increase in ART coverage= 1.49 (95% C.I: 1.07 – 2.08)

Acquired drug resistance in low- and middle-income countries

According to data from 36 WHO surveys of acquired HIV drug resistance assessing more than 5000 people in 12 low- and middle-income countries between 2007 and 2010, the prevalence of HIV drug resistance to any drug among people starting antiretroviral therapy ranged from 4.8% (95% 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 treatment success (viral load suppression). Among people with virological failure, 72% had resistance, mostly to nucleoside reverse transcriptase inhibitors (NRTI) and NNRTI drugs. The remaining 28% had no resistance mutations and therefore experienced treatment failure for other reasons, such as very poor adherence or extended treatment interruptions, and may have been switched to costlier second-line regimens unnecessarily.

The resistance patterns observed among people failing first-line treatment after 12 months suggest that, if these people were switched to second-line regimens soon after virological failure, standard second-line therapies (consisting of two nucleoside class drugs and a boosted protease inhibitor) would be effective in achieving viral load suppression in the majority of cases.

In total, about 18% of the people being treated were lost to follow-up or experienced treatment failure without resistance mutations being detected. Given the likelihood of treatment interruptions, these people have a high probability of harbouring a drug-resistant virus. Therefore, the true prevalence of HIV drug resistance could be considerably higher than the levels detected in the surveys. This underscores the need for active defaulter tracing, improved patient monitoring and adherence counselling.

Monitoring for prevention

Key to preventing HIV drug resistance is the routine monitoring of programmatic factors known to favour its emergence. WHO's global HIV drug resistance surveillance and monitoring strategy recommends using a minimum set of HIV drug resistance early warning indicators in all treatment sites to identify factors known to be associated with HIV drug resistance that require improvement, so that corrective action can be taken at the clinic and/or programme level. The indicators assess:

- how well populations are adherent to therapy (on-time pill pick-up);
- whether pharmacies dispense regimens that are likely to promote the emergence of HIV drug resistance, such as mono- or dual therapy (dispensing practices);
- whether stock-outs of routinely dispensed antiretroviral medicines occur (drug supply continuity); and
- the extent to which people are retained in care at the antiretroviral clinic-level.

Monitoring of an additional indicator, viral load suppression at 12 months, is recommended at sites where viral load testing is routinely performed.

Since 2004, 50 countries have piloted the monitoring of these indicators at select clinics. Although global trends or conclusions cannot be extrapolated from these data, a considerable proportion of clinics were found to have important gaps in service delivery and programme performance, particularly with respect to procurement and supply systems, adherence and clinic retention.

Conclusions

As the coverage of antiretroviral therapy continues to grow, there are signs of increased transmitted drug resistance in the areas surveyed. Among individuals receiving antiretroviral therapy, acquired drug resistance continues to hamper treatment effectiveness. Nevertheless, available data suggest that, despite the rapid expansion of treatment coverage, increases in HIV drug resistance have occurred within expected levels in the areas surveyed, and no changes in antiretroviral treatment guidelines are warranted at the moment.

Concerted action is needed to preserve the future effectiveness of antiretroviral therapy. Treatment programmes should monitor the quality of the services they deliver by using the early warning indicators for HIV drug resistance and undertaking immediate corrective action when performance problems are detected. In addition, programmes should perform routine surveillance of HIV drug resistance among people experiencing treatment failure and among recently-infected populations. Despite intensive efforts, routine HIV drug resistance surveillance has not kept pace with the scale-up of treatment in many countries, limiting the ability to reliably assess trends over time. WHO, through its partner network of collaborating institutions, is committed to monitoring HIV drug resistance globally and to advocating for expanded routine surveillance using standardized methods and increased mobilization of national and international funds to support HIV drug resistance surveillance.

1. INTRODUCTION

1.1 Overview

Combination antiretroviral therapy for HIV infection has saved millions of lives since it was introduced. As coverage of antiretroviral therapy continues to grow, some degree of emergence and transmission of HIV drug resistance is inevitable. Significant population-level HIV drug resistance could potentially restrict future therapeutic options and increase treatment costs by requiring new and more expensive antiretroviral regimens. However, as the experiences of many countries demonstrate, HIV drug resistance can be monitored and steps can be taken to minimize its emergence.

In simple terms, HIV drug resistance refers to the ability of HIV to replicate in the presence of drugs that usually suppress its replication. HIV drug resistance is caused by changes (mutations) in the virus's genetic structure. Mutations are very common in HIV because the virus replicates very rapidly and does not contain the proteins needed to correct the mistakes it makes during this process. As such, some degree of HIV drug resistance is anticipated to occur among people receiving treatment even when appropriate regimens are provided and optimal adherence is achieved *(1)*. Transmitted HIV drug resistance occurs when previously uninfected individuals are infected with drug-resistant virus, and acquired HIV drug resistance develops when mutations emerge due to viral replication in individuals receiving antiretroviral therapy.

This report aims to generally assess the levels of transmitted and acquired drug resistance in select geographical areas of low- and middle-income countries. It is based on two distinct data sources: surveys performed to assess transmitted and acquired drug resistance using standardized WHO methods (WHO surveys) and a broad systematic review of the published literature on transmitted and acquired drug resistance. Findings from the monitoring of early warning indicators of HIV drug resistance are also presented and discussed.

1.2 Structure of the report

This report is organized as follows.

Chapter 1 outlines the objectives of the report, discusses the determinants of HIV drug resistance, and describes the WHO global HIV drug resistance surveillance and monitoring strategy.

Chapter 2 provides an overview of HIV drug resistance in high-income countries.

Chapter 3 discusses a systematic review and meta-analysis of the published literature on levels and trends of *transmitted* drug resistance in select areas of low- and middle-income countries and presents data from surveys of transmitted drug resistance conducted according to standardized WHO methods.

Chapter 4 discusses a systematic review of levels of *acquired* drug resistance in patients failing first-line antiretroviral therapy in select low- and middle-income countries, and presents data from surveys of acquired drug resistance conducted according to standardized WHO methods.

Chapter 5 presents findings from the monitoring of early warning indicators of HIV drug resistance.

Chapter 6 discusses overall conclusions.

Annex 1 presents detailed notes on the methods used to generate and interpret the data contained in this report.

Annex 2 provides supplemental data and tables from WHO HIV drug resistance surveys.

1.3 Determinants of HIV drug resistance[1]

Factors contributing to the selection of HIV drug resistance can be broadly grouped into four categories: ❶ regimen- and drug-specific, ❷ virus-related, ❸ patient-specific and ❹ programmatic.

1.3.1 Regimen- and drug-specific factors

The genetic barrier of an antiretroviral therapy regimen, defined as the number of key mutations required to overcome drug-selective pressure, is an important factor in the emergence of HIV drug resistance. First-line regimens recommended by WHO for adults and adolescents typically include one non-nucleoside reverse-transcriptase inhibitor (NNRTI), either nevirapine (NVP) or efavirenz (EFV), combined with two nucleoside reverse-transcriptase (NRTI) backbone drugs, typically zidovudine or tenofovir, combined with either lamivudine or emtricitabine *(3)*.

1 This section relies extensively on: Bertagnolio et al. *(2)*.

Although the efficacy of these regimens has been well established *(4–7)* in both high-income and low- and middle-income countries *(8–10)*, a recognized limitation of NNRTI-based regimens is their relatively lower genetic barrier to resistance compared with regimens using boosted protease inhibitors (bPI) in place of non-nucleosides. Although NNRTI-based regimens differ with respect to their genetic barrier, which is influenced by the accompanying NRTI component *(5,11–13)*, they select significantly more resistance than bPI-based regimens among people experiencing treatment failure despite similar rates of virological suppression *(14,15)*.

Suboptimal regimens, such as single-dose nevirapine for preventing mother-to-child transmission, and inappropriate prescribing practices resulting in the use of single and two-drug antiretroviral therapy regimens, can further increase the risk of developing HIV drug emergence *(16)*.

Interactions between drugs can favour the selection of HIV drug resistance by reducing the concentration of antiretroviral drugs to suboptimal levels. Rifampicin, for example, has been shown to reduce the levels of nevirapine between 20% and 58% and efavirenz by 26% *(17,18)*. In addition, populations exposed to antiretroviral drugs before initiation first-line antiretroviral therapy are also more likely to carry pre-treatment resistance *(19)*, leading to more rapid virological failure and further acquisition of HIV drug resistance *(20,21)*.

The use of complex regimens with a high pill burden also reduces adherence, thus favouring the selection of HIV drug resistance *(22,23)*. In contrast, the use of fixed-dose combinations can improve adherence, facilitate rational prescribing and streamline drug procurement *(23)*.

1.3.2 Virus factors

Evidence of pre-treatment HIV drug resistance is strongly associated with virological failure and further acquisition of resistance after the first year of NNRTI-based first-line antiretroviral therapy *(20,24,25)*. Research has shown that individuals with transmitted HIV drug resistance are expected to accumulate more NRTI resistance at the time of virological failure, leading to a growing number being treated with a boosted PI and two NRTI with partial or no activity at the time of switch to second-line therapy *(26)*.

Moreover, the frequency and characteristics of mutation patterns may also differ across virus subtypes. For example, after exposure to single-dose nevirapine, more HIV drug resistance is observed in HIV-1 subtype D than in subtype A *(27)*. Recent data suggest that increased rates of K65R acquisition in HIV-1 subtype C may be caused by the nature of the subtype C RNA template *(28)*.

1.3.3 Patient factors

Adherence to antiretroviral therapy is well recognized as an essential component of individual and programmatic treatment success. Poor adherence to antiretroviral therapy is a predictor of virological failure *(29–33)*, emergence of HIV drug resistance, disease progression *(34–36)* and death *(37–39)*. Hence, sustained scale up of antiretroviral therapy depends on the ability of programmes to deliver care in a way that minimizes treatment interruptions through drug supply continuity and maximizes adherence.

At the individual level, studies suggest that untreated depression, active substance abuse, poor insight into disease and treatment, being an adolescent or young adult, a higher pill burden, more frequent dosing and forgetfulness are associated with poor adherence *(40)*. Adherence can be especially challenging among children for a variety of reasons, including drug formulations and palatability *(41–43)*. In addition, children are at greater risk of acquiring drug resistance, since they often depend on caregivers for their treatment *(44)*. If caregivers are themselves unwell, they may not be able to attend clinic visits with the child, collect medication as needed or provide them with their medication on schedule. Orphans living with HIV frequently face the greatest challenges in terms of adherence. Although orphans in institutional care typically have high levels of adherence (since trained caregivers often provide care), those who are raised in the households of relatives have poorer outcomes and are more likely to default or be non-adherent to care *(45)*.

Adherence may also be negatively affected by HIV-associated stigma and discrimination *(46,47)*. Notably, people living with HIV may fear that taking medication in the presence of others may inadvertently disclose their HIV status, thus deterring them from adequately following the regimens prescribed *(48)*.

1.3.4 Programmatic factors

Programme-level factors, such as limited human resources, inadequate infrastructure and weak supply management systems, can also negatively affect treatment adherence and retention in care and facilitate the emergence of population-level HIV drug resistance.

The provision of chronic HIV care is still a challenge for most health systems in low- and middle-income countries as it requires robust and integrated systems to support adherence and trace individuals with unknown treatment

outcomes. Overcrowding and understaffing of antiretroviral therapy clinics may further aggravate these constraints by reducing the time dedicated for counselling and the reinforcement of adherence messages. Research suggests that reducing the quality and intensity of patient monitoring by antiretroviral therapy clinics may decrease retention, leading to higher proportions of treatment interruptions and more people with unknown treatment outcomes *(49)*.

Moreover, fragile drug procurement and supply management systems can result in drug stock-outs and missed antiretroviral drug doses *(50–52)*. Cost and structural barriers, such as food insecurity and out-of-pocket expenditure for transport or monitoring tests, can equally lead to treatment interruptions and suboptimal adherence *(53,54)*.

The absence of routine viral load monitoring, which is a more sensitive indicator of treatment failure than clinical and immunological parameters, may lead some people to experience prolonged periods of virological failure before changing regimen *(3,55)*. Although current modelling of antiretroviral therapy effectiveness has not reached a consensus with respect to the implementation of systematic viral load monitoring in low- and middle-income countries *(56–59)*, maintaining people on a failing NNRTI-based regimens leads to the accumulation of multiple NRTI mutations *(60)*.

1.4 WHO's global HIV drug resistance surveillance and monitoring strategy

Understanding the emergence and transmission of population-level HIV drug resistance and the interaction between its various determinants require routine surveillance, monitoring and evaluation, and operational research.

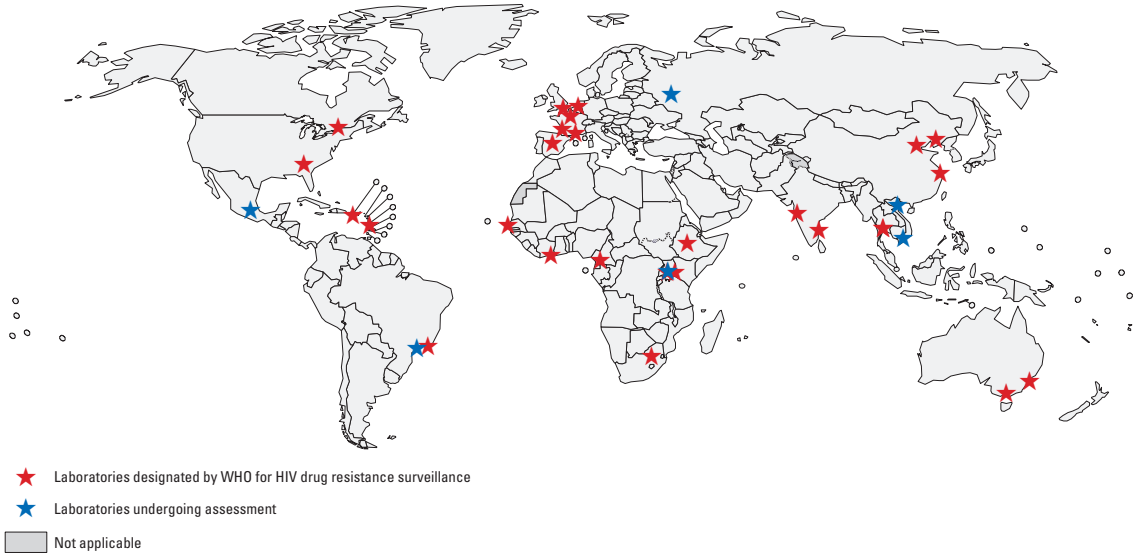
To adequately monitor the emergence of drug resistance, WHO spearheaded the establishment of the global HIV Drug Resistance Network (HIVResNet), comprised of more than 50 international institutions, experts and national HIV programme representatives. In collaboration with HIVResNet and with support from the Bill & Melinda Gates Foundation, WHO developed a global HIV drug resistance surveillance and monitoring strategy *(61)*. The strategy was designed to inform decision-making on the optimal choice of antiretroviral regimens and to identify any programmatic adjustments needed to minimize the emergence of HIV drug resistance. The strategy has three main assessment elements: (1) surveillance of transmitted HIV drug resistance in recently infected populations, (2) surveillance of acquired HIV drug resistance in populations receiving antiretroviral therapy and (3) monitoring of early warning indicators of HIV drug resistance *(61)*.

1. **Surveillance of transmitted HIV drug resistance in recently infected populations** *(62)* (Chapter 3). The WHO survey method for assessing transmitted HIV drug resistance classifies resistance prevalence as low (below 5%), moderate (between 5% and 15%) or high (over 15%) in recently infected populations in a specific geographical area *(62,63)*. Whenever possible, these surveys use remnant specimens from the populations of interest (e.g., young pregnant women) and data from regularly performed serosurveys that estimate HIV prevalence, which are already in place in most countries. Transmitted HIV drug resistance surveys alert programme planners to the existence of transmission of drug-resistant HIV, and the results may inform the selection of current regimens for preventing mother-to-child transmission and future first-line antiretroviral therapy regimens.

2. **Surveillance of acquired HIV drug resistance in populations receiving antiretroviral therapy** *(64)* (Chapter 4). WHO prospective surveys of acquired HIV drug resistance are performed at sentinel antiretroviral therapy clinics and estimate the prevalence and patterns of HIV drug resistance in adult and paediatric populations experiencing antiretroviral therapy failure *(64)*. At each sentinel survey clinic, a cohort of people initiating first-line therapy is formed. HIV drug resistance genotyping is performed on people initiating antiretroviral therapy, and HIV-RNA is quantified at the time that treatment is switched to second-line or 12 months after antiretroviral therapy initiation for people remaining on first-line treatment. For people with detectable virus (more than 1000 copies/ml), genotyping is performed to characterize drug resistance mutations. A threshold of 1000 copies/ml has been chosen to characterize treatment failure because of the sensitivity and reproducibility of standard commercial genotyping assays. Survey results provide site-specific assessments of viral load suppression, which are particularly relevant to clinics and programmes in which viral load is not routinely performed.[1]

1 The data presented herein were obtained from the implementation of this protocol. However, a cross-sectional approach to assessing acquired drug resistance has been developed and is currently being piloted in Namibia (see Section 7 in Annex 1).

Figure 1.1 HIV drug resistance testing laboratories designated for public health surveillance by the WHO, 2011



Monitoring of early warning indicators for HIV drug resistance *(61)* (Chapter 5). Early warning indicators monitor factors at individual clinics known to create situations favourable to the emergence of HIV drug resistance. Without requiring drug resistance testing, the monitoring of early warning indicators provides the context for interpreting the results from surveys of transmitted and acquired HIV drug resistance. The timely identification of clinics with suboptimal performance helps tailor appropriate interventions that can potentially optimize care and treatment and reduce the risk of population-level HIV drug resistance emergence.

In addition to these three key assessment elements, WHO has developed a comprehensive HIV drug resistance laboratory strategy, which includes laboratory membership and rigorous quality assurance of genotyping data to support public health surveillance *(65)*. As of 2011, 27 testing laboratories for HIV drug resistance had been granted membership (Figure 1.1).

1.5 Note on data sources and methods

Aggregate levels and trends discussed in the meta-analyses performed based on data from published studies on transmitted and acquired drug resistance (excluding WHO surveys) should be considered in light of the heterogeneity of study methods and countries assessed. Many of the studies included were performed using distinct methods and may differ with respect to the population assessed (such as recent or chronic infections), sampling frame (such as consecutive, convenient or random selection from the general population) and the laboratory methods used (such as dried blood spot or plasma specimens and the genotyping methods used).

Individual studies may also have been influenced by factors such as antiretroviral therapy coverage, variation in HIV subtypes, quality of care at antiretroviral therapy programmes and sites, country income levels and the structure or organization of health services. Therefore, prevalence estimates may not be nationally or regionally representative. Moreover, studies included in the meta-analyses reported resistance data according to any of the internationally recognized drug resistance mutation lists. Therefore variation in how mutations were defined may have influenced individual study results and, hence, aggregate analyses. This may be the case particularly for estimates of PI resistance.

The number of low- and middle-income countries with available data on HIV drug resistance remains limited. This implies that the results and conclusions presented in this report may be biased towards programmes with above-average performance, as the implementation of surveys and/or studies on drug resistance can itself indicate above-average concern with programmatic quality and treatment success.

Although early warning indicators of HIV drug resistance were designed to be nationally representative, reported results reflect a pilot and scale-up phase and are therefore unlikely to be typical of a country's antiretroviral treatment programme functioning. WHO surveys to assess transmitted and acquired drug resistance are not intended to be nationally representative. Additionally, areas surveyed varied considerably, among countries and across time, so generalizations may not be appropriate or applicable. Nevertheless, their results should be interpreted as an alert to programme managers that resistance transmission and acquisition are occurring in specific geographical areas of a country and that, depending on observed levels, wider policy action may be warranted.

Regions refer, unless otherwise noted, to WHO's standard regional grouping *(66)*. As this report focuses on low- and middle-income countries, the term "Latin America and the Caribbean" is used instead of Region of the Americas. For the purposes of this report, subregional groupings for the WHO African Region (central, eastern, southern and western Africa) are used to highlight, when appropriate, patterns applicable or specific to a subset of countries (Section 1 in Annex 1 provides detailed sub-regional country grouping). Asia refers to countries in the South-East Asia Region and Western Pacific Region combined. All confidence intervals quoted are at the 95% level.

REFERENCES

1. Richman DD et al. The prevalence of antiretroviral drug resistance in the United States. *AIDS,* 2004, 18:1393–1401.
2. Bertagnolio S et al. Determinants of HIV drug resistance and public health implications in low- and middle-income countries. *Antiviral Therapy*, in press.
3. *Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. 2010 revision.* Geneva, World Health Organization, 2010 (http://www.who.int/hiv/pub/arv/adult2010/en/index.html, accessed 28 June 2012).
4. Gallant JE et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA*, 2004, 292:191–201.
5. Soria A et al. Resistance profiles after different periods of exposure to a first-line antiretroviral regimen in a Cameroonian cohort of HIV type-1–infected patients. *Antiviral Therapy*, 2009, 14:339–347.
6. Gallant JE et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *New England Journal of Medicine,* 2006, 354:251–260.
7. Smith CJ et al. The rate of viral rebound after attainment of an HIV load <50 copies/ml according to specific antiretroviral drugs in use: results from a multicenter cohort study. *Journal of Infectious Diseases*, 2005, 192:1387–1397.
8. Braitstein P et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet*, 2006, 367:817–824.
9. Nachega JB et al. Efavirenz versus nevirapine-based initial treatment of HIV infection: clinical and virological outcomes in southern African adults. *AIDS*, 2008, 22:2117–2125.
10. Palombi L et al. Incidence and predictors of death, retention, and switch to second-line regimens in antiretroviral- treated patients in sub-Saharan African sites with comprehensive monitoring availability. *Clinical Infectious Diseases*, 2009, 48:115–122.
11. Margot NA et al. Development of HIV-1 drug resistance through 144 weeks in antiretroviral-naive subjects on emtricitabine, tenofovir disoproxil fumarate and efavirenz compared with lamivudine/zidovudine and efavirenz in study GS-01-934. *Journal of Acquired Immune Deficiency Syndromes*, 2009, 52:209–221.
12. Maserati R et al. Emerging mutations at virological failure of HAART combinations containing tenofovir and lamivudine or emtricitabine. *AIDS*, 2010, 24:1013–1018.
13. Svicher V et al. Different evolution of genotypic resistance profiles to emtricitabine versus lamivudine in tenofovir-containing regimens. *Journal of Acquired Immune Deficiency Syndromes*, 2010, 55:336–344.
14. Cozzi-Lepri A et al. The rate of accumulation of nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance in patients kept on a virologically failing regimen containing an NNRTI. *HIV Medicine*, 2012, 13:62–72.
15. Gupta R et al. Emergence of drug resistance in HIV type 1-infected patients after receipt of first-line highly active antiretroviral therapy: a systematic review of clinical trials. *Clinical Infectious Diseases,* 2008, 47:712–722.
16. Chomat AM et al. Knowledge, beliefs, and health care practices relating to treatment of HIV in Vellore, India. *AIDS Patient Care and STDs*, 2009, 23:477–484.
17. Maartens G, Decloedt E, Cohen K. Effectiveness and safety of antiretrovirals with rifampicin: crucial issues for high-burden countries. *Antiviral Therapy*, 2009, 14:1039–1043.
18. Boulle A et al. Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. *JAMA*, 2008, 300:530–539.
19. Andreotti M et al. Resistance mutation patterns in plasma and breast milk of HIV-infected women receiving highly-active antiretroviral therapy for mother-to-child transmission prevention. *AIDS*, 2007, 21:2360–2362.
20. Wittkop L et al. Effect of transmitted drug resistance on virological and immunological response to initial combination antiretroviral therapy for HIV (EuroCoord-CHAIN joint project): a European multicohort study. *Lancet Infectious Diseases,* 2011, 377:1580–1587.
21. Jordan MR. Assessments of HIV drug resistance mutations in resource-limited settings. *Clinical Infectious Diseases*, 2011, 52:1058–1060.
22. Maggiolo F et al. Once-a-day therapy for HIV infection: a controlled, randomized study in antiretroviral-naive HIV-1-infected patients. *Antiviral Therapy*, 2003, 8:339–346.
23. Juday T et al. Factors associated with complete adherence to HIV combination antiretroviral therapy. *HIV Clinical Trials*, 2011, 12:71–78.
24. Sigaloff KC et al. High prevalence of transmitted antiretroviral drug resistance among newly HIV type 1 diagnosed adults in Mombasa, Kenya. *AIDS Research and Human Retroviruses*, 2012 [Epub ahead of print].
25. Hamers RL et al. Effect of pretreatment HIV-1 drug resistance on immunological, virological, and drug-resistance outcomes of first-line antiretroviral treatment in sub-Saharan Africa: a multicentre cohort study. *Lancet Infectious Diseases*, 2011, 12:307–317.
26. Bartlett JA et al. Lopinavir/ritonavir monotherapy after virologic failure of first-line antiretroviral therapy in resource-limited settings. *AIDS*, 2012, Epub 2012/03/24.
27. Hauser A et al. Emergence and persistence of minor drug-resistant HIV-1 variants in Ugandan women after nevirapine single-dose prophylaxis. *PLoS One*, 2011, 6:e20357.
28. McColl DJ et al. Prevalence, genotypic associations and phenotypic characterization of K65R, L74V and other HIV-1 RT resistance mutations in a commercial database. *Antiviral Therapy*, 2008, 13:189–197.
29. Lucas GM, Chaisson RE, Moore RD. Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. *Annals of Internal Medicine*, 1999, 131:81–87.
30. Nachega JB et al. Adherence to nonnucleoside reverse transcriptase inhibitor-based HIV therapy and virologic outcomes. *Annals of Internal Medicine*, 2007, 146:564–573.

31. Arnsten JH et al. Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: comparison of self-report and electronic monitoring. *Clinical Infectious Diseases,* 2001, 33:1417–1423.
32. Shuter J et al. HIV-infected patients receiving lopinavir/ritonavir-based antiretroviral therapy achieve high rates of virologic suppression despite adherence rates less than 95%. *Journal of Acquired Immune Deficiency Syndromes*, 2007, 45:4–8.
33. Martin M et al. Relationship between adherence level, type of the antiretroviral regimen, and plasma HIV type 1 RNA viral load: a prospective cohort study. *AIDS Research and Human Retroviruses*, 2008, 24:1263–1268.
34. Bangsberg DR et al. Adherence-resistance relationships for protease and non-nucleoside reverse transcriptase inhibitors explained by virological fitness. *AIDS*, 2006, 20:223–231.
35. Harrigan PR et al. Predictors of HIV drug-resistance mutations in a large antiretroviral-naive cohort initiating triple antiretroviral therapy. *Journal of Infectious Diseases*, 2005, 191:339–347.
36. Bangsberg DR et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS*, 2001, 15:1181–1183.
37. Hogg RS et al. Intermittent use of triple-combination therapy is predictive of mortality at baseline and after 1 year of follow-up. *AIDS*, 2002, 16:1051–1058.
38. Nachega JB et al. Adherence to highly active antiretroviral therapy assessed by pharmacy claims predicts survival in HIV-infected South African adults. *Journal of Acquired Immune Deficiency Syndromes*, 2006, 43:78–84.
39. Wood E et al. Impact of baseline viral load and adherence on survival of HIV-infected adults with baseline CD4 cell counts ≤ 200 cells/μl. *AIDS*, 2006, 20:1117–1123.
40. Mills EJ et al. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. *JAMA*, 2006, 296:679–690.
41. Foster C et al. Young people in the United Kingdom and Ireland with perinatally acquired HIV: the pediatric legacy for adult services. *AIDS Patient Care and STDs*, 2009, 23:159–166.
42. Temple ME, Koranyi KI, Nahata MC. Gastrostomy tube placement in nonadherent HIV-infected children. *Annals of Pharmacotherapy,* 2001, 35:414–418.
43. King JR et al. Pharmacokinetics of antiretrovirals administered to HIV-infected children via gastrostomy tube. *HIV Clinical Trials*, 2004, 5:288–293.
44. Nahirya Ntege P et al. Tablets are more acceptable and give fewer problems than syrups among young HIV-infected children in resource limited settings in the ARROW trial. *2nd International Workshop on HIV Paediatrics, 16–17 July 2010 and XVIII International AIDS Conference, 18–23 July 2010, Vienna, Austria* (http://pag.aids2010.org/Abstracts.apsx?AID=13055, accessed 28 June 2012).
45. Nyandiko WM et al. Outcomes of HIV-infected orphaned and non-orphaned children on antiretroviral therapy in western Kenya. *Journal of Acquired Immune Deficiency Syndromes*, 2006, 43:418–425.
46. Rintamaki LS et al. Social stigma concerns and HIV medication adherence. *AIDS Patient Care and STDs*, 2006, 20:359–368.
47. Nachega JB et al. Adherence to antiretroviral therapy in HIV-infected adults in Soweto, South Africa. *AIDS Research and Human Retroviruses*, 2004, 20:1053–1056.
48. Tamabc V et al. "It is not that I forget, it's just that I don't want other people to know": barriers to and strategies for adherence to antiretroviral therapy among HIV patients in northern Viet Nam. *AIDS Care: Psychological and Socio-medical Aspects of AIDS/HIV*, 2011, 23:139–145.
49. Cornell M et al. Temporal changes in programme outcomes among adult patients initiating antiretroviral therapy across South Africa, 2002–2007. *AIDS*, 2010, 24:2263–2270.
50. Oyugi JH et al. Treatment interruptions predict resistance in HIV-positive individuals purchasing fixed-dose combination antiretroviral therapy in Kampala, Uganda. *AIDS*, 2007, 21:965–971.
51. Marcellin F et al. Determinants of unplanned antiretroviral treatment interruptions among people living with HIV in Yaounde, Cameroon (EVAL survey, ANRS 12-116). *Tropical Medicine and International Health*, 2008, 13:1470–1478.
52. Eholie SP et al. Field adherence to highly active antiretroviral therapy in HIV-infected adults in Abidjan, Côte d'Ivoire. *Journal of Acquired Immune Deficiency Syndromes,* 2007, 45:355–358.
53. Crane JT et al. The price of adherence: qualitative findings from HIV positive individuals purchasing fixed-dose combination generic HIV antiretroviral therapy in Kampala, Uganda. *AIDS Behavior,* 2006, 10:437–442.
54. Weiser S et al. Barriers to antiretroviral adherence for patients living with HIV infection and AIDS in Botswana. *Journal of Acquired Immune Deficiency Syndromes*, 2003, 34:281–288.
55. Keiser O et al. Switching to second-line antiretroviral therapy in resource-limited settings: comparison of programmes with and without viral load monitoring. *AIDS*, 2009, 23:1867–1874.
56. Phillips AN et al. Effect on transmission of HIV-1 resistance of timing of implementation of viral load monitoring to determine switches from first to second-line antiretroviral regimens in resource-limited settings. *AIDS*, 2011, 25:843–850.
57. Fox MP et al. High rates of survival, immune reconstitution, and virologic suppression on second-line antiretroviral therapy in South Africa. *Journal of Acquired Immune Deficiency Syndromes*; 2010, 53:500–506.
58. Pujades-Rodriguez M et al. Treatment failure and mortality factors in patients receiving second-line HIV therapy in resource-limited countries. *JAMA*, 2010, 304:303–312.
59. Hamers RL et al. Cost-effectiveness of laboratory monitoring for management of HIV treatment in sub-Saharan Africa: a model-based analysis. *AIDS*, 2012 [Epub ahead of print].
60. Hosseinipour MC et al. The public health approach to identify antiretroviral therapy failure: high-level nucleoside reverse transcriptase inhibitor resistance among Malawians failing first-line antiretroviral therapy. *AIDS*, 2009, 23:1127–1134.

61. Bennett DE et al. The World Health Organization's global strategy for prevention and assessment of HIV drug resistance. *Antiviral Therapy*, 2008, 13(Suppl. 2):1–13.
62. Bennett DE et al. Recommendations for surveillance of transmitted HIV drug resistance in countries scaling up antiretroviral treatment. *Antiviral Therapy*, 2008, 13(Suppl. 2):25–36.
63. Myatt M, Bennett DE. A novel sequential sampling technique for the surveillance of transmitted HIV drug resistance by cross-sectional survey for use in low resource settings. *Antiviral Therapy*, 2008, 13(Suppl. 2):37–48.
64. Jordan MR et al. World Health Organization surveys to monitor HIV drug resistance prevention and associated factors in sentinel antiretroviral treatment sites. *Antiviral Therapy*, 2008, 13(Suppl. 2):15–23.
65. Bertagnolio S et al. World Health Organization/HIVRestNet Drug Resistance Laboratory Strategy. *Antiviral Therapy*, 2008, 13(Suppl. 2):49–57).
66. WHO – its people and offices [web site]. Geneva, World Health Organization, 2012 (http://www.who.int/about/structure/en/index.html, accessed 28 June 2012).

2. HIV DRUG RESISTANCE IN HIGH-INCOME COUNTRIES

KEY FINDINGS

- Available data suggest that between 10% and 17% of ARV-naïve patients in Europe, United States, Japan and Australia have drug resistance to at least one antiretroviral.
- With respect to acquired drug resistance, evidence indicates that (i) the proportion of patients achieving full viral suppression has increased over time, thus minimizing the emergence of acquired drug resistance and its subsequent transmission and that (ii) resistance to NRTI is the most frequently observed type in patients failing antiretroviral therapy, followed by NNRTI and PI resistance.

Highly active antiretroviral therapy has been available in most high-income countries since its introduction in the late 1990s. Another feature of HIV treatment programmes in high-income countries is the widespread use of drug resistance genotyping to support case management and treatment monitoring. Despite important structural and socioeconomic differences, their experiences can be informative for low- and middle-income countries scaling up access to antiretroviral therapy.

2.1 Drug resistance in ARV-naïve recently or chronically-infected populations

Available data suggest that between 10% and 17% of ARV-naïve individuals in Europe, the United States, Japan and Australia have drug resistance to at least one antiretroviral drug.

In Europe, a comprehensive review of 75 studies on transmitted drug resistance published in 2009 covering 23 209 people from 20 countries estimated the prevalence of transmitted drug resistance at 10.9%. Drug resistance most frequently involved NRTI, with a prevalence of 7.4%. The prevalence for NNRTI and PI was 3.4% and 2.9%, respectively *(1)*.[1] Levels of transmitted drug resistance seem to have declined significantly over time, from 11.5% between 1985 and 2003 to 7.7% between 2004 and 2009. This reduction was largely caused by drops in the levels of NRTI resistance, from 8.0% to 4.3%, and of PI resistance, from 3.3% to 1.4%. In contrast, the prevalence of NNRTI resistance changed only slightly over the same period, from 2.9% to 3.2%. A study of 25 cohorts from across Europe between 1998 and 2009 found broadly similar results. In a group of 10 056 antiretroviral therapy–naive people, 954, or 9.5%, had at least one drug resistance mutation *(2)*.

In the United States, a study from the Center for AIDS Research (National Institutes of Health) with 14 111 people covering the period from before 2003 through 2008 reported an overall genotypic resistance prevalence of 14.2% to at least one drug (8.3% NNRTI, 8.2% NRTI, 4.2% PI) *(3)*. In the states of Washington and Colorado, the overall prevalence of drug resistance was 17% (11% NNRTI, 6% NRTI, 3% PI) among 506 people with recent or established HIV infection *(4)*, while in San Francisco, 16% of 372 people diagnosed between 2002 and 2009 with acute or early HIV infection had drug resistance to at least one antiretroviral drug *(5)*. In 2006, among 2030 newly diagnosed individuals from 10 states and 1 county health department in the United States, mutations associated with HIV drug resistance were found in 14.6% (NNRTI 7.8%, NRTI 5.6%, PI 4.5%). A broader review of 45 studies conducted between 1993 and 2008 (42 in the United States and 3 in Canada) found that, among 8718 people, about 12.9% carried HIV drug resistance. Resistance to NRTI, at 7.4%, was observed to be highest, followed by resistance to NNRTI and PI, with 5.7% and 3.2%, respectively *(1)*. In contrast to Europe, the review suggests that prevalence of HIV drug resistance may have increased in North America from 11.6% before 2001 to 14.3% after 2003, driven largely by the increase in NNRTI resistance, from 4.1% to 8.3%, with NRTI resistance decreasing from 8.0% to 6.4%.

In Japan, the prevalence of drug resistance mutations in people newly diagnosed with HIV-1 infection doubled from 5.9% in 2003 to 11.9% in 2010 *(6,7)*, and the relative prevalence of resistance by drug class changed considerably

1 Most studies do not differentiate between recently or chronically infected individuals.

over this period. Before 2007, resistance to NRTI was higher than to NNRTI and PI, but since 2007 resistance to PI has become most prevalent, reaching 4.9% in 2010. In contrast to reports from other high-income countries, transmitted NNRTI resistance seems to be less frequent in Japan.

In Australia, research conducted between 1992 and 2001 in Sydney in a group of 185 recently-infected individuals found levels of transmitted drug resistance to reverse-transcriptase inhibitors peaking in the mid-1990s, dropping significantly with the introduction of combination therapy in 1996 and then reaching a plateau of 10–15% during the years 1999–2001 *(8)*. More recently, an assessment of drug resistance among 466 recently infected individuals between 1996 and 2007 in the Victoria region found an average annual transmitted drug resistance prevalence of 16%, predominantly associated with NRTI and NNRTI *(9)*. Mutations known to cause resistance to PI remained uncommon.

2.2 Acquired drug resistance

Data on acquired drug resistance in high-income countries suggest that NRTI resistance is the most frequent form of drug resistance in people for whom antiretroviral therapy is failing, followed by NNRTI and PI resistance.

Among 1988 people failing antiretroviral therapy between 2000 and 2004 from 15 European countries, 80.7% had at least one drug resistance mutation (NRTI 75.5%, NNRTI 48.5%, PI 35.8%). Predicted resistance to most bPI was estimated at less than 25% *(10)*. Similar results were observed in an assessment of 16 511 drug resistance genotypes from 11 492 treatment-experienced individuals in seven European countries between 1999 and 2008: 80.1% had at least one drug resistance mutation (NRTI 67.2%, NNRTI 53.7%, PI 32.4%), with 17.2% showing resistance to three classes *(11)*. After adjusting for confounding factors, people failing therapy in more recent calendar years showed a decline in overall resistance to NRTI and PI but not to NNRTI.

Though evidence is still limited and additional research is needed, other studies have also observed this downward trend in the prevalence of acquired drug resistance. This finding is probably associated with the use of improved first- and second-line regimens with greater potential to fully suppress viral replication. Among 5422 individuals in British Columbia, the incidence of drug resistance in those receiving antiretroviral therapy dropped more than 12-fold between 1996 and 2008, and viral suppression increased from 64.7% in 2000 to 87.7% in 2008 *(12)*. In an HIV outpatient study, the frequency of HIV resistance among people receiving antiretroviral therapy for at least four months with plasma viral load above 1000 copies/ml dropped from 88% in 1999 to 79% in 2008, with a statistically significant decline observed in the incidence of acquired drug resistance for PI.

REFERENCES

1. Frentz D, Boucher CA, van de Vijver DA. Temporal changes in the epidemiology of transmission of drug-resistant HIV-1 across the world. *AIDS Reviews*, 2012, 14:17–27.
2. Wittkop L et al. Effect of transmitted drug resistance on virological and immunological response to initial combination antiretroviral therapy for HIV (EuroCoord-CHAIN joint project): a European multicohort study. *Lancet Infectious Diseases*, 2011, 11:363–371.
3. Poon et al. Transmitted drug resistance in the CFAR network of integrated clinical systems cohort: prevalence and effects on pre-therapy CD4 and viral load. *PLoS One*, 2011, 6:e21189.
4. Markovitz AR et al. Primary antiretroviral drug resistance in newly human immunodeficiency virus-diagnosed individuals testing anonymously and confidentially. *Microbial Drug Resistance*, 2011, 17:283–289.
5. Jain V et al. Transmitted drug resistance in persons with acute/early HIV-1 in San Francisco, 2002–2009. *PLoS One*, 2010, 5:e15510.
6. Hattori J et al. Surveillance of drug resistance and phylodynamic network analysis of newly infected HIV/AIDS patients: Japan, 2003 to 2010. *19th Conference on Retroviruses and Opportunistic Infections, 5–8 March 2012, Seattle, WA, USA* (Paper 729; http://www.retroconference.org/2012b/Abstracts/44128.htm, accessed 28 June 2012).
7. Hattori J et al. Trends in transmitted drug-resistant HIV-1 and demographic characteristics of newly diagnosed patients: nationwide surveillance from 2003 to 2008 in Japan. *Antiviral Research*, 2010, 88:72–79.
8. Ammaranond P et al. No increase in protease resistance and a decrease in reverse transcriptase resistance mutations in primary HIV-1 infection: 1992–2001. *AIDS*, 2003, 17:264–267.
9. Russell JS et al. Prevalence of transmitted HIV drug resistance since the availability of highly active antiretroviral therapy. *Communicable Disease Intelligence*, 2009, 33:216–220.
10. van de Vijver DA et al. HIV-1 drug-resistance patterns among patients on failing treatment in a large number of European countries. *Acta Dermatovenerologica Alpina, Panonica, et Adriatica*, 2010, 19:3–9.
11. Prosperi MC et al. Detection of drug resistance mutations at low plasma HIV-1 RNA load in a European multicentre cohort study. *Journal of Antimicrobial Chemotherapy*, 2011, 66:1886–1896.
12. Gill VS et al. Improved virological outcomes in British Columbia concomitant with decreasing incidence of HIV type 1 drug resistance detection. *Clinical Infectious Diseases*, 2010, 50:98–105.

3. TRANSMITTED HIV DRUG RESISTANCE IN LOW- AND MIDDLE-INCOME COUNTRIES

KEY FINDINGS

1. Available data suggest that the estimated prevalence of transmitted drug resistance increased between 2003 and 2010 in the areas surveyed, although within expected levels.

- A systematic review of published studies in ARV-naïve recently- or chronically-infected individuals (excluding WHO surveys) found that more recent surveys reported higher average levels of HIV drug resistance, reaching an estimated high of 6.6% (95% confidence interval 5.1%–8.3%)[a] in 2009.

- Pooled analysis of data from WHO surveys indicates that the estimated prevalence of transmitted HIV drug resistance to NNRTI increased between 2004 and 2010. This estimated increase was particularly apparent in the areas surveyed in the African region, where the prevalence of NNRTI resistance reached 3.4% (95% CI 1.8%–5.2%) in 2009.

2. Data from WHO surveys suggest that greater coverage of antiretroviral therapy was associated with a higher prevalence of transmitted drug resistance, particularly to NNRTI, although the estimated effect on drug resistance of an increase in antiretroviral therapy coverage remained modest in the areas surveyed.

a All confidence intervals quoted are at the 95% level.

3.1 Overview

Transmitted HIV drug resistance occurs when previously uninfected individuals are infected with drug-resistant virus. The term transmitted HIV drug resistance is appropriately applied only to HIV drug resistance detected in recently infected individuals because, over time and at variable rates, mutations may revert to wild-type, become archived in viral DNA or fall below the sensitivity level of standard genotyping assays to detect them *(1)*. However, most published studies also include individuals who may have been infected for a considerably longer time and are considered to be "chronically infected".

To assess levels and trends of transmitted HIV drug resistance in recently and chronically infected individuals in low- and middle-income countries, the published literature was systematically reviewed, and the main findings are presented below.

3.2 Literature review on drug resistance among ARV-naïve recently- or chronically-infected populations

A systematic literature search identified 126 articles, spanning 40 countries, comprising a total of 16 650 people living with HIV (Table 3.1). Studies were considered if they included untreated recently or chronically infected individuals 15 years and older and had more than 10 genotypes available. Section 3 in Annex 1 provides additional details on the methods used. Table 1 in Annex 1 lists the studies included. Geographically, most studies matching the predefined selection criteria were in Africa, followed by Latin America and the Caribbean, the Western Pacific Region and the South-East Asia Region.[1]

Many of the studies included in this meta-analysis were performed using distinct methods and may differ with respect to the population studied (such as recent or chronic infections), the sampling frame (such as consecutive, convenient or random selection from the general population) and the laboratory methods used (such as

1 Data from low- and middle-income countries in the European Region and the Eastern Mediterranean Region were excluded from the analysis due to the paucity of available data.

dried blood spots or plasma specimens and the genotyping methods used). Thus, prevalence estimates may not be nationally or regionally representative.

Data from individual studies were abstracted and aggregated by region and year and revealed that more recent studies reported higher levels of HIV drug resistance, reaching a high of 6.6% (95% CI 5.1%-8.3%) in 2009. Most of this change was due to an associated increase in the overall prevalence of mutations conferring resistance to NNRTI. No evidence of increasing resistance over time to NRTI or PI was observed (Table 3.2).

In the Africa region, although overall prevalence levels did not appear to vary significantly over time (Table 1 in Annex 2), a more detailed analysis by drug class showed a statistically significant increase in the prevalence of NNRTI mutations. The prevalence of NNRTI resistance in 2003 was 1% (95% CI 0.3%–2.1%) and 6.4% (95% CI 1.3%–17.5%) in 2010 in the region. NRTI resistance varied little over time. Reported resistance to PI was generally stable and low, as the vast majority of people living with HIV in this region received an NNRTI-based first-line regimen during the period studied.

Prevalence estimates for general or class-specific mutations did not vary significantly in studies conducted in the South-East Asia or Western Pacific regions between 2003 and 2010. However, HIV drug resistance increased significantly in Latin America and the Caribbean, a fact that is probably associated, among other reasons, with the earlier introduction and higher coverage of antiretroviral therapy in the region. Table 1 in Annex 2 provides a regional breakdown of resistance prevalence.

3.3 WHO surveys to assess transmitted drug resistance

WHO recommends a minimum-resource method to assess transmitted HIV drug resistance in specific geographical areas of resource-limited countries where transmitted HIV drug resistance is likely to be seen first (such as in urban areas where antiretroviral therapy has been available for at least a few years). If HIV drug resistance transmission is low in such areas, it is unlikely to be higher elsewhere in the country.

The survey method for transmitted HIV drug resistance samples individuals from populations likely to be antiretroviral drug-naive and to have been recently infected. Section 4 in Annex 1 provides additional information on survey methods

Table 3.1 Studies included in the systematic review of drug resistance among ARV-naïve recently- or chronically-infected populations, by region and by year of survey, 2003–2010

	Number of surveys							
	2003	2004	2005	2006	2007	2008	2009	2010
Total number of studies	20	16	17	18	20	15	16	4
African Region	9	9	10	5	11	7	7	1
Western/Central	2	4	4	1	7	1	1	–
Southern	2	2	3	3	3	2	4	–
Eastern	5	3	3	1	1	4	2	1
South-East Asia Region	3	–	2	5	2	1	–	2
Western Pacific Region	–	2	3	5	4	1	3	1
Latin American and the Caribbean	8	5	2	3	3	6	6	–
Total number of countries represented	14	12	11	11	13	13	8	3
Number of individuals genotyped	2281	1777	3568	1735	2572	3078	1503	136

Table 3.2 Estimated prevalence of HIV drug resistance among ARV-naive individuals from the published literature, 2003–2010

	% with at least one drug resistance mutation (95% confidence interval)								
	2003	2004	2005	2006	2007	2008	2009	2010	P-value[a]
Any	3.6 (2.3-5.2)	4.5 (2.3-7.3)	1.9 (0.9-3.3)	2.5 (1.2-4.1)	3.1 (1.6-5.0)	4.9 (3.6-6.3)	6.6 (5.1-8.3)	2.1 (0.1-5.8)	0.03
NRTI	2.0 (0.9-3.4)	2.3 (1.0-4.0)	0.7 (0.1-1.5)	0.9 (0.1-2.2)	1.2 (0.4-2.4)	1.9 (1.1-2.9)	2.0 (0.8-3.5)	0.0 (0.0-1.4)	0.46
NNRTI	0.9 (0.2-2.0)	1.0 (0.2-2.1)	1.1 (0.4-2.0)	1.2 (0.3-2.7)	1.2 (0.5-2.2)	1.8 (1.3-2.4)	3.3 (2.3-4.4)	0.9 (0.0-4.8)	<0.001
PI	0.3 (0.0-1.0)	0.9 (0.2-2.0)	0.0 (0.0-0.1)	0.0 (0.0-0.3)	0.2 (0.0-0.6)	0.7 (0.3-1.4)	0.9 (0.2-1.9)	0.0 (0.0-1.4)	0.48

a Statistical methods are described in Section 3, Annex 1.

for transmitted HIV drug resistance. This method is not intended to provide a point prevalence estimate but rather to classify transmitted resistance for each drug class as low (prevalence less than 5%), moderate (prevalence between 5% and 15%) or high (prevalence more than 15%). Surveys are not designed to be nationally representative or to assess trends over time. Instead, their main purpose is to alert programme managers that resistance is being transmitted in specific geographical areas of a country and that, depending on their results, wider policy action may be warranted. Therefore, survey results can be instrumental in informing not only the selection of future first-line antiretroviral therapy regimens but also in optimizing approaches for preventing mother-to-child transmission of HIV as well as for pre- and post-exposure prophylaxis.

3.3.1 Overview

Between 2004 and 2010, 30 countries initiated 101 surveys using the WHO-recommended method to assess transmitted drug resistance. Data from 82 surveys from 30 countries were made available to WHO. HIV drug resistance

Figure 3.1 Countries (n=26) reporting results from WHO surveys of transmitted HIV drug resistance, 2004–2010

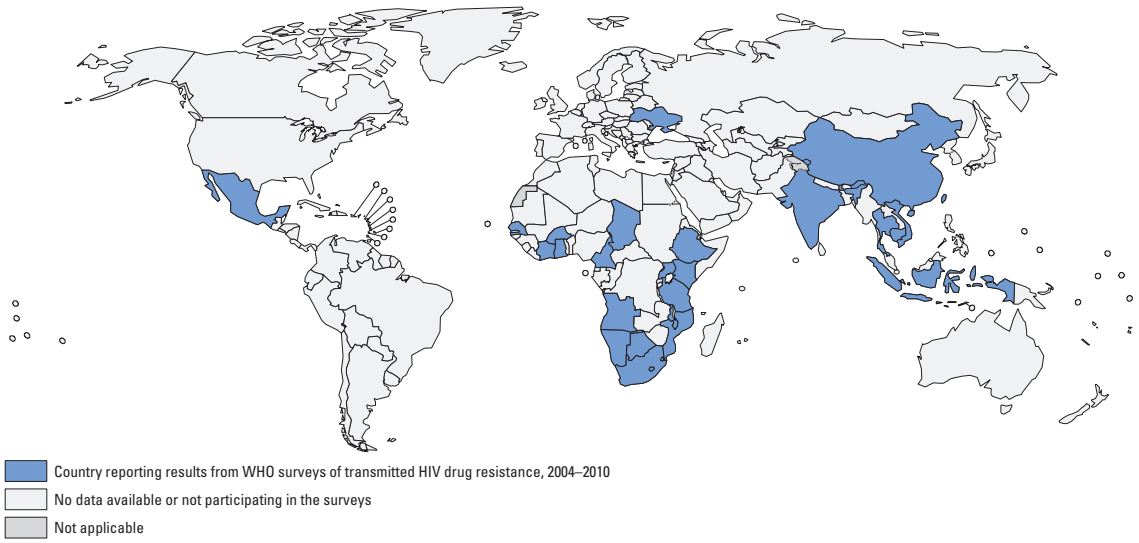
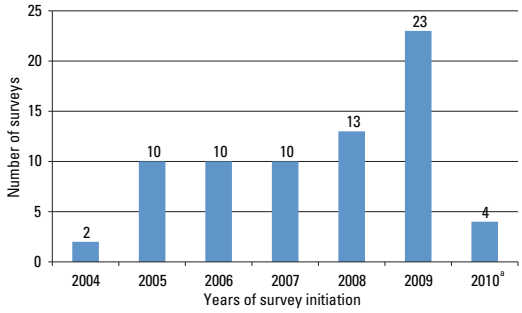


Figure 3.2 Number of WHO transmitted HIV drug resistance surveys with classifiable results for at least one drug class, 2004–2010 (n = 72)



a Fourteen surveys were implemented in 2010; however, only four had results available for analysis.

prevalence could be classified as low, moderate or high for at least one drug class in a subset of 72 surveys conducted in 26 countries (Figures 3.1 and 3.2, and Table 3.3).[1] Section 2 in Annex 1 summarizes methods for sequence data analysis and quality assurance.

Table 2 in Annex 2 provides individual survey results. Ten surveys (not shown) had insufficient sample sizes to allow their results to be classified into any of the three prevalence categories (low, moderate or high); nevertheless, their patient-level data were included in the pooled analysis presented in section 3.3.3.[2]

Overall, 91.7% of the 72 surveys with classifiable results were conducted between 2005 and 2009. Geographically, most (59.7%, or 43/72) surveys were implemented in the African Region.

WHO recommends that surveys be repeated every two years to detect signs of increasing transmission of resistance. Of the 18 countries reporting from Africa, 10 conducted surveys only in one year, whereas 8 repeated them over time with variable frequency: 4 countries implemented it in two different years (Botswana, Burkina Faso, Kenya and Mozambique), three repeated it three times in different years (Malawi, Swaziland and Uganda) and South Africa conducted the surveys annually. Table 3 in Annex 2 lists countries with at least two surveys repeated over time.

Of the 11 countries comprising the WHO South-East Asia Region, only three (India, Indonesia and Thailand) reported results, for a total of six surveys, all of which were conducted before 2007. Thailand repeated the survey twice in different years, whereas India and Indonesia implemented the survey only once.

1 In three surveys the sample size was insufficient to classify resistance into one of the three categories (<5%, 5%–15% or >15%) but was sufficient to classify resistance as being above 5% (Phnom Penh, Cambodia, 2008 (NNRTI), KwaZulu-Natal, South Africa, 2008 (NNRTI and NRTI) and Kyiv, Ukraine, 2009 (NRTI). These surveys were therefore considered as having a moderate prevalence of HIV drug resistance (between 5% and 15%).

2 These surveys were conducted in Botswana, Gaborone, 2007; Burundi, Bujumbura, 2007; Cambodia, multiple areas, 2006; Cambodia, Phnom Penh, 2006; Central African Republic, Bangui, 2007; Congo, Brazzaville, 2006; Congo, Pointe Noire, 2006; Islamic Republic of Iran, multiple areas, 2006; Mozambique, Maputo, 2007; and South Africa, Western Cape, 2007.

Eighteen surveys were conducted in the Western Pacific Region in three countries (Cambodia, China and Viet Nam), mostly between 2008 and 2009. China implemented 15 surveys between 2007 and 2008 in multiple geographical areas, and Viet Nam performed two surveys, one in Hanoi (2006) and one in Ho Chi Minh City (2007). In the European Region and in Latin America and the Caribbean, only one country in each, Ukraine and Mexico, respectively, implemented surveys according to WHO methods. Most of the countries in these regions have concentrated or low-level epidemics, and the implementation of transmitted HIV drug resistance surveys using current methods, designed to be applied in the context of generalized HIV epidemics, was particularly challenging.[1]

Of the 72 surveys, 41 (56.9%) were conducted in antenatal care sites among pregnant women, and most included only women in their first pregnancy – to minimize the likelihood of including women with previous exposure to regimens for preventing mother-to-child transmission – and younger than 25 years of age – to minimize the likelihood of including individuals with chronic infection and with prior exposure to antiretrovirals. Twenty-eight (38.8%) were conducted in voluntary counselling and testing sites, chiefly among men and women younger than 25 years of age. One survey was conducted among sex workers (Kampala, Uganda, 2008), one among people who inject drugs (Jakarta, Indonesia, 2006) and one among blood donors (Bangkok, Thailand, 2005).

3.3.2 Classification of WHO surveys on transmitted HIV drug resistance

Table 3.4 summarizes the results of the 72 surveys that could be classified as low, moderate or high prevalence for at least one drug class. Of the 72 surveys, 52 (72.2%) had a low prevalence classification to all drug classes. No survey was classified as having a high prevalence of transmitted HIV drug resistance. However, 20 (27.8%) had a moderate prevalence classification of resistance to one or more antiretroviral drug class (NRTI and/or NNRTI and/or PI). Because of their important implications for programme management and service delivery, surveys showing moderate prevalence of drug resistance merit particular attention.

Almost two thirds (60% or 12 of 20) of the surveys with a moderate prevalence classification reported a moderate level of resistance to NNRTI, 50% (10 of 20) to NRTI, and 10% (2 of 20) to PI.

1 Other surveys may have been conducted but data were not reported or made available for inclusion in this analysis.

Table 3.3 Number of WHO surveys of transmitted HIV drug resistance with results classifiable for at least one drug class, by year of implementation and geographical region, 2004–2010

	Number of surveys							
Geographical region	2004	2005	2006	2007	2008	2009	2010	Total
African Region	1	8	8	5	6	11	4	43
Eastern		3	2	1	1	6	1	14
Ethiopia		1						1
Kenya		1				1		2
Malawi			1			2	1	4
Mozambique				1		2		3
Uganda			1		1	1		3
United Republic of Tanzania		1						1
Southern	1	4	3	3	3	4	3	21
Angola						1		1
Botswana		2		1				3
Lesotho						1		1
Namibia			1					1
South Africa	1	2	1	2	2	2	2	12
Swaziland			1		1		1	3
Western/Central		1	3	1	2	1		8
Burkina Faso		1				1		2
Cameroon			2					2
Chad			1					1
Côte d'Ivoire					1			1
Ghana					1			1
Senegal				1				1
Latin America and the Caribbean	1							1
Mexico	1							1
European Region						4		4
Ukraine						4		4
South-East Asia Region		2	1	3				6
India				2				2
Indonesia			1					1
Thailand		2		1				3
Western Pacific Region			1	2	7	8		18
Cambodia					1			1
China				1	6	8		15
Viet Nam			1	1				2
Overall	2	10	10	10	13	23	4	72

Table 3.4 Results of WHO transmitted HIV drug resistance surveys

Category of transmitted HIV drug resistance	Drug class	N (%) of surveys
Low prevalence (<5%)	All	52 (72.2%)
Moderate prevalence (5%–15%)	Any	20 (27.8%)
	Only NNRTI	8 (11.1%)
	Only NRTI	7 (9.7%)
	Only PI	1 (1.4%)
	NRTI and NNRTI	3 (4.2%)
	NNRTI and PI	1 (1.4%)
	NRTI and PI	0 (0%)
High prevalence (>15%)	Any	0 (0%)
Total number of surveys		72

Table 3.5 WHO surveys of transmitted HIV drug resistance with moderate prevalence classification (5%–15%), by year, 2004–2010

Year	Total surveys	Number of surveys (% of annual total) with classification 5%–15% for at least 1 drug class
2004	2	2 (100%)
2005	10	0 (0%)
2006	10	2 (20%)
2007	10	2 (20%)
2008	13	3 (23%)
2009	23	9 (39%)
2010	4	2 (50%)
Total	72	20 (28%)

Table 3.6 Frequency of WHO surveys reporting moderate prevalence of transmitted HIV drug resistance, by period (before or after 2007)[a]

		Number (%) of surveys with moderate (5–15%) prevalence			
Year	Total surveys	Any drug class	NNRTI	NRTI	PI
2004–2006	22	4 (18%)	1 (5%)	3 (14%)	0 (0%)
2007–2010	50	16 (32%)	11 (22%)	7 (14%)	2 (4%)

a Mid-point period.

Table 3.7 WHO surveys of transmitted HIV drug resistance in selected areas, 2004–2010[a]

Country	Geographical area	2004	2005	2006	2007	2008	2009	2010
Botswana	Francistown							
Malawi	Lilongwe						NNRTI	NNRTI
South Africa	Gauteng	NRTI						
South Africa	KwaZulu-Natal					NNRTI +NRTI	NNRTI	NNRTI +NRTI
Swaziland	Manzini-Mbambane corridor							
Uganda	Entebbe/Kampala[b]						NRTI	
China	Beijing							
China	Hunan						NNRTI	
China	Liangshan (Sichuan)							
China	Shenzhen							

a Green: low prevalence classification of transmitted HIV drug resistance; red: moderate prevalence classification of transmitted HIV drug resistance.

b Entebbe/Kampala are considered as being part of the same geographic area

Between 2004 and 2010, the proportion of surveys reporting a moderate prevalence of transmitted HIV drug resistance to at least one drug class increased from 18.2% (4 of 22) in 2004–2006 to 32% (16 of 50) in 2007–2010 (Tables 3.5 and 3.6). This increase was mostly driven by a considerable rise in the number of surveys reporting moderate prevalence of NNRTI resistance. In contrast, the frequency of surveys reporting a moderate prevalence of resistance to NRTI remained stable.

Geographically, the overall increase in the frequency of surveys with moderate prevalence appears to be caused by increased reports of moderate prevalence classification in the Africa Region, where the proportion of surveys reporting moderate prevalence rose from 17.6% (3 of 17) in 2004–2006 to 40.7% (11 of 27) in 2007–2010.

Overall, 65% (13 of 20) of the surveys showing a moderate prevalence of transmitted HIV drug resistance to any drug class were in the African Region, particularly in eastern Africa (30%, 6 of 20). Five (25%, 5 of 20) were conducted in the Western Pacific Region, one in Latin America and the Caribbean and another in the European Region. No survey from the South-East Asia Region showed resistance between 5% and 15%. Table 4 in Annex 2 describes the geographical distribution of surveys with moderate classification.

Of the two surveys reporting moderate prevalence of transmitted HIV drug resistance to PI, one was in Eastern Africa and one in the Western Pacific Region. Of the three surveys with moderate prevalence of resistance for both NNRTI and NRTI, two were from countries in southern Africa and one in Western/Central Africa.

Globally, in the 11 geographical areas in which surveys were repeated over time (see Table 3.7) and therefore allowed a more detailed analysis, four reported a change from low to moderate prevalence, signalling an increase in transmission of drug-resistant virus (Lilongwe in Malawi, Entebbe/Kampala in Uganda, KwaZulu-Natal in South Africa, and Hunan in China). Two surveys conducted in Beira (Mozambique) in 2007 and 2009 showed moderate levels of transmitted HIV drug resistance to NNRTI and NRTI, respectively. In contrast, in five geographical areas, successive surveys confirmed a low prevalence of transmitted HIV drug resistance.

Moderate prevalence of transmitted HIV drug resistance was reported in Gauteng (South Africa) in 2004, followed by five consecutive surveys documenting low prevalence (Box 3.1).

Box 3.1 Assessing transmitted drug resistance in the provinces of KwaZulu-Natal and Gauteng, South Africa

South Africa initiated the roll-out of antiretroviral therapy nationally in 2004. In the province of KwaZulu-Natal, surveys to assess the prevalence of transmitted drug resistance were implemented in 2005 and repeated annually between 2007 and 2010 (Table 3.8). The prevalence of transmitted drug resistance was low in 2005 and 2007. However, the prevalence of transmitted HIV drug resistance to NNRTI was found to be moderate in 2008, 2009 and 2010. Similarly, the prevalence of transmitted HIV drug resistance to NRTI also increased to moderate in 2008 and 2010.

In Gauteng province, seven surveys of transmitted HIV drug resistance among women pregnant for the first time were conducted between 2004 and 2010. In this region, all surveys in all years showed low prevalence of resistance for all drug classes except for a moderate prevalence classification of NRTI resistance in 2004. While such result may represent a true moderate prevalence estimate, it may also have been caused by random misclassification error, as it was observed in the year when antiretroviral therapy was being rolled out and coverage was expected to be low. The survey may also have captured women infected with drug-resistant virus from partners participating in early clinical trials or whose virus had been exposed to drugs in other settings (private unregulated market). Nevertheless, subsequent surveys in Gauteng documented low prevalence of transmitted HIV drug resistance to all drug classes.

Antiretroviral therapy programme functioning should be investigated to address why moderate levels of transmitted HIV drug resistance were observed more frequently in KwaZulu-Natal compared with Gauteng. Specifically, factors known to be associated with HIV drug resistance such as loss to follow-up, retention, adherence, drug supply continuity, rates of population-level viral load suppression and prescribing practices should be assessed.

Table 3.8 Results of surveys to assess transmitted drug resistance in the provinces of KwaZulu-Natal and Gauteng (South Africa), 2004–20 10

	KwaZulu-Natal		
Year	NNRTI	NRTI	PI
2005	nc	<5%	nc
2007	<5%	<5%	<5%
2008	5-15%	5-15%	<5%
2009	5-15%	<5%	<5%
2010	5-15%	5-15%	<5%

nc= not classifiable (insufficient specimens available to classify transmitted HIV drug resistance)

	Gauteng		
Year	NNRTI	NRTI	PI
2004	<5%	5-15%	nc
2005	<5%	<5%	nc
2006	<5%	<5%	<5%
2007	<5%	<5%	<5%
2008	<5%	<5%	<5%
2009	<5%	<5%	<5%
2010	<5%	<5%	<5%

3.3.3 Pooled analysis

To assess whether transmitted HIV drug resistance increased over time in the areas surveyed, sequence data from all 82 surveys – a total of 3588 recently infected individuals – were pooled. Figure 3.3 describes the regional distribution of individuals included in the pooled analysis. Figure 3.4 provides a breakdown by the type of population surveyed.

In this sample, a statistically significant increase in the prevalence of transmitted drug resistance to NNRTI was observed between 2004 and 2010, particularly in the areas surveyed in the African Region (Table 3.9). Section 9 in Annex 1 provides additional details on the statistical methods used. Section 2 in Annex 1 summarizes methods for sequence data analysis and quality assurance.

Figure 3.3 Regional distribution of individuals from pooled analysis

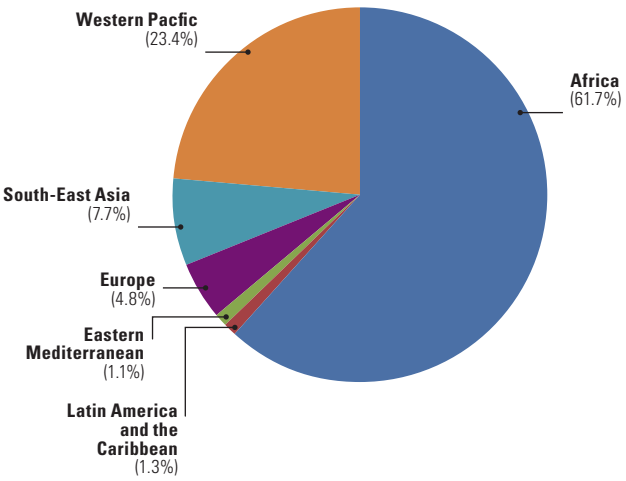


Figure 3.4 Populations surveyed (% of total number of individuals from pooled analysis)

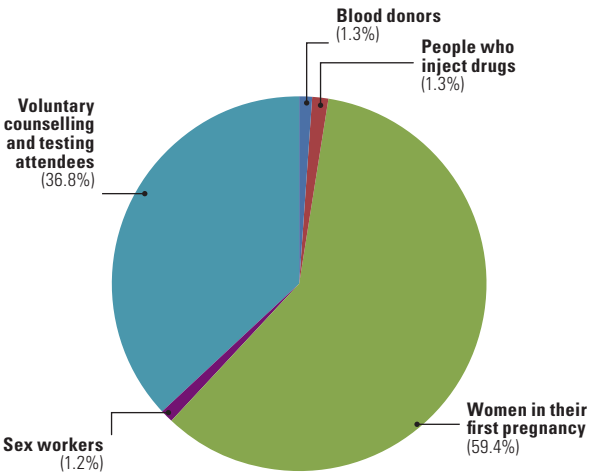
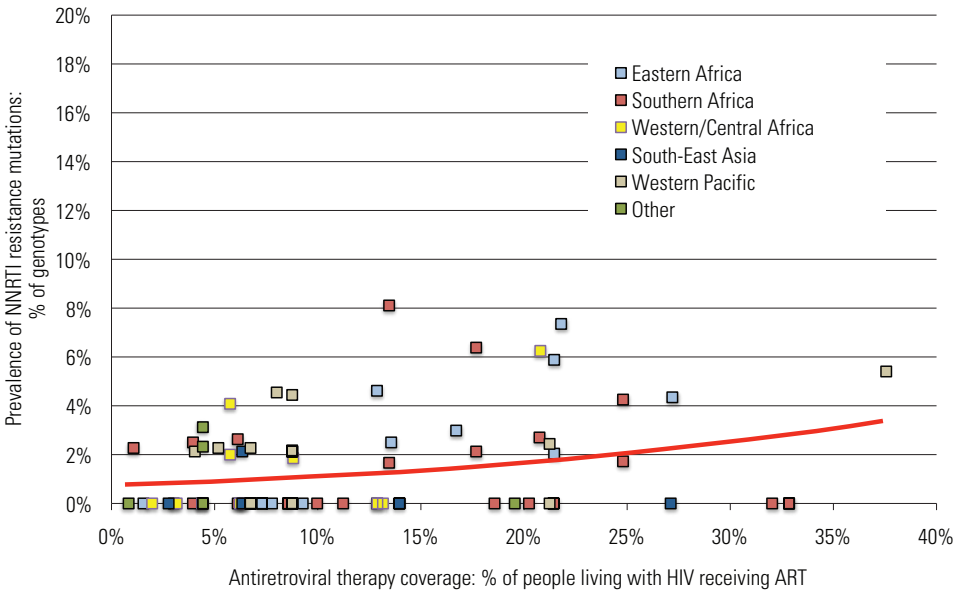


Table 3.9 Estimates of transmitted HIV drug resistance by year of survey, region and antiretroviral therapy class (WHO transmitted HIV drug resistance surveys), 2004–2010[c]

	2004[a]	2005	2006	2007	2008	2009	2010[a]	P-value[b] (adjusted for region)
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	
Any Drug								
African Region	10.0 (2.8–23.7)	0.2 (0.0–1.4)	0.6 (0.0–2.4)	1.2 (0.1–3.2)	1.8 (0.1–4.8)	4.5 (2.3–7.2)	2.8 (0.1–7.7)	0.04
South-East Asia Region	—	0.7 (0.0–4.8)	2.2 (0.1–11.8)	1.0 (0.2–3.8)	—	—	—	—
Western Pacific Region	—	—	4.5 (1.0–9.6)	4.4 (1.1–9.4)	1.5 (0.0–4.3)	2.4 (0.6–4.8)	—	0.41
Latin America and the Caribbean	8.5 (2.4–20.4)	—	—	—	—	—	—	—
Europe Region	—	—	—	—	—	2.6 (0.1–6.9)	—	—
Eastern Mediterranean Region	—	—	7.7 (1.6–20.9)	—	—	—	—	—
Overall	9.2 (3.7–16.4)	0.3 (0.2–1.4)	1.6 (0.4–3.2)	1.6 (0.5–3.1)	1.6 (0.3–3.5)	3.4 (2.1–5.1)	2.8 (0.1–7.7)	0.06
NNRTI								
African Region	2.3 (0.1–12.0)	0.0 (0.0–1.0)	0.1 (0.0–0.9)	0.0 (0.0–0.7)	1.5 (0.1–3.9)	3.4 (1.8–5.2)	2.0 (0.2–5.0)	<0.01
South-East Asia Region	—	0.0 (0.0–2.3)	0.0 (0.0–7.9)	0.3 (0.0–2.6)	—	—	—	—
Western Pacific Region	—	—	1.4 (0.1–5.1)	3.6 (0.6–8.2)	0.5 (0.2–2.1)	0.9 (0.0–2.6)	—	0.41
Latin America and the Caribbean	0.0 (0.0–7.5)	—	—	—	—	—	—	—
Europe Region	—	—	—	—	—	0.8 (0.3–3.4)	—	—
Eastern Mediterranean Region	—	—	0.0 (0.0–9.0)	—	—	—	—	—
Overall	0.7 (0.0–4.3)	0.0 (0.0–0.8)	0.2 (0.1–0.9)	0.3 (0.0–1.3)	0.9 (0.1–2.2)	2.0 (1.1–3.2)	2.0 (0.2–5.0)	<0.01
NRTI								
African Region	4.5 (0.6–15.5)	0.0 (0.0–0.7)	0.1 (0.0–1.1)	0.7 (0.0–2.5)	0.5 (0.2–2.0)	0.9 (0.2–2.2)	0.6 (0.0–3.7)	0.24
South-East Asia Region	—	0.7 (0.0–5.0)	0.0 (0.0–7.9)	0.0 (0.0–1.5)	—	—	—	—
Western Pacific Region	—	—	1.4 (0.1–5.1)	0.6 (0.0–3.6)	0.3 (0.0–1.8)	0.6 (0.0–2.1)	—	0.71
Latin America and the Caribbean	8.5 (2.4–20.4)	—	—	—	—	—	—	—
Europe Region	—	—	—	—	—	1.2 (0.2–4.6)	—	—
Eastern Mediterranean Region	—	—	7.7 (1.6–20.9)	—	—	—	—	—
Overall	6.5 (2.0–12.8)	0.0 (0.0–0.8)	0.5 (0.0–1.4)	0.4 (0.0–1.4)	0.4 (0.0–1.4)	0.9 (0.3–1.7)	0.6 (0.0–3.7)	0.37
PI								
African Region	2.8 (0.1–14.5)	0.2 (0.0–1.5)	0.0 (0.0–0.5)	0.3 (0.0–1.6)	0.0 (0.0–0.8)	0.4 (0.0–1.4)	0.0 (0.0–1.1)	0.76
South-East Asia Region	—	0.0 (0.0–2.2)	2.3 (0.1–12.0)	0.3 (0.0–2.5)	—	—	—	—
Western Pacific Region	—	—	2.7 (0.1–7.3)	0.6 (0.0–3.6)	0.2 (0.0–1.6)	0.8 (0.0–2.3)	—	0.34
Latin America and the Caribbean	0.0 (0.0–7.5)	—	—	—	—	—	—	—
Europe Region	—	—	—	—	—	0.2 (0.0–2.4)	—	—
Eastern Mediterranean Region	—	—	0.0 (0.0–9.0)	—	—	—	—	—
Overall	0.7 (0.0–5.3)	0.1 (0.0–1.1)	0.2 (0.0–1.0)	0.3 (0.0–1.3)	0.0 (0.0–0.7)	0.5 (0.0–1.2)	0.0 (0.0–1.1)	—

a Results may have been affected by the limited amount of data available and should be interpreted cautiously (87 specimens in 2004 and 196 in 2010).
b Some P-values could not be calculated due to collinearity, lack of data and/or variability. Statistical methods are described in Section 9, Annex 1.
c Areas surveyed varied considerably among countries and across time.
— Data are not available or applicable.

Figure 3.5 Relationship between antiretroviral therapy coverage and prevalence of transmitted NNRTI drug resistance mutations



Areas surveyed varied considerably, among countries and across time, so generalizations may not be appropriate or applicable. Nevertheless, in a subset of six geographical areas in the African Region in which transmitted HIV drug resistance surveys were repeated in different years, three areas reported a change from low to moderate prevalence of transmitted HIV drug resistance (Lilongwe in Malawi, Entebbe/Kampala in Uganda and KwaZulu-Natal in South Africa), signalling an increase in the transmission of drug-resistant virus in these areas (Table 3.7).

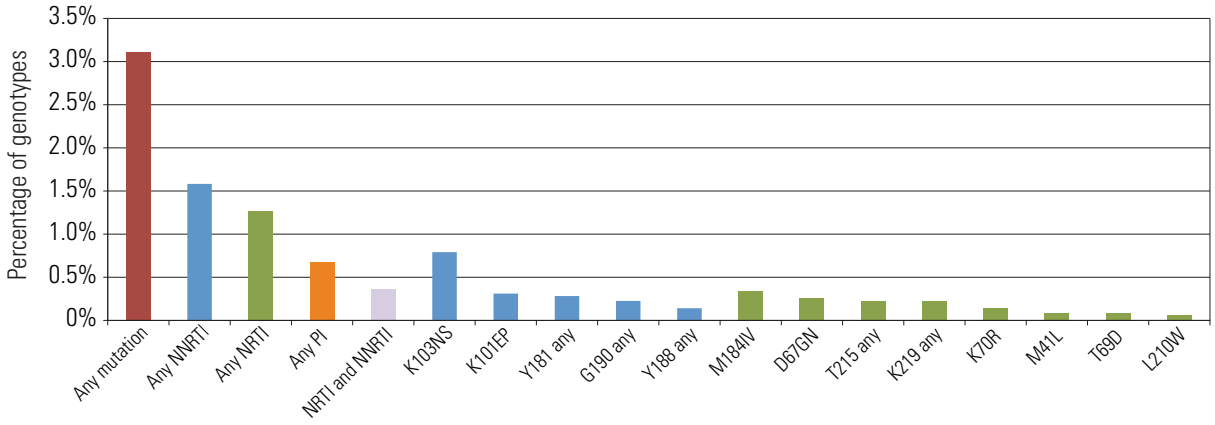
Fig. 3.5 depicts the relationship between the prevalence of transmitted NNRTI drug resistance mutations and antiretroviral therapy coverage. Antiretroviral therapy coverage was defined as the number of people living with HIV receiving antiretroviral drugs in the country in which the survey was undertaken divided by the total number of people living with HIV. Controlling for regional variability, available data indicate that higher levels of antiretroviral therapy coverage are associated, though modestly, with increased prevalence of transmitted drug resistance to NNRTI (p-value adjusted for region= 0.039; odds ratio= 1.49, 95% CI 1.07–2.08).

Although such an increase remained within expected levels, this finding is particularly critical in the context of the expanded use of antiretroviral drugs not only for treatment but also for the prevention of HIV infection. Unless carefully monitored and contained, transmitted drug resistance can potentially reduce the efficacy of standard antiretroviral therapy – an issue aggravated by the limited availability of alternative antiretroviral drug regimens.

3.3.4 Prevalence of HIV drug resistance mutations

Figure 3.6 shows the prevalence of drug resistance mutations across all 82 surveys performed between 2004 and 2010. For the description of the mutation list used, see Section 5 in Annex 1. Overall, 3.1% of the individuals surveyed had transmitted drug resistance to at least one drug class. As expected, NNRTI mutations *(2)* were most commonly observed (1.6%), followed by NRTI (1.3%) and PI (0.7%). Only 0.4% of individuals had both NNRTI and NRTI drug resistance mutations. Among individual mutations, those at position 103 (K103N or S) were the most common (0.8%), followed by D67N or G, K101E or P, Y181C, and M184V, ranging from 0.3% to 0.4%. Only one sequence carried K65R, a mutation conferring resistance to tenofovir.

Figure 3.6 Prevalence of drug resistance mutations in individuals included in WHO transmitted HIV drug resistance surveys, 2004–2010



Red: percentage of individuals with any drug resistance mutation as defined by the WHO 2009 Surveillance HIV Drug Resistance mutation list *(2)*.

Blue: any NNRTI mutation.

Green: any NRTI mutation.

Orange: any PI mutation.

Lavender: both NRTI and NNRTI mutations.

Details of which mutations were observed most commonly are displayed on the right in blue for NNRTI and in green for NRTI mutations. Alternative variants at each position are combined: for example, K103NS represents people with K103N or K103S; "any" designates multiple variants at that position (for example, T215 any includes D, F, I, N, S and Y). A total of 3381 PR genotypes and 3539 RT genotypes are included; the total number of genotypes (n=3588) was used as the denominator for calculating the prevalence of "any mutation".

REFERENCES

1. Pingen M et al. Evolutionary pathways of transmitted drug-resistant HIV-1. *Journal of Antimicrobial Chemotherapy*, 2011, 66:1467–1480.
2. Bennett DE et al. Drug resistance mutations for surveillance of transmitted HIV-1 drug-resistance: 2009 update. *PLoS One*, 2009, 4:e4724.

4. ACQUIRED DRUG RESISTANCE IN LOW- AND MIDDLE-INCOME COUNTRIES

KEY FINDINGS

1. SYSTEMATIC LITERATURE REVIEW

A systematic review of the published literature indicates that, in eight low- and middle-income countries in Asia and sub-Saharan Africa, 60% of the 573 people failing NNRTI-based first-line therapy after a median of 12 months had resistance to any HIV drug class. The remaining 40% failed with no HIV drug resistance, suggesting that very poor adherence or extended treatment interruption could have played an important role in causing virological failure.

2. WHO SURVEYS TO ASSESS ACQUIRED DRUG RESISTANCE

Resistance before initiation of first-line antiretroviral therapy

- Forty surveys, comprising 6370 people, were performed in 12 countries between 2006 and 2010 using a standardized WHO protocol to assess acquired drug resistance. In a pooled analysis of people initiating first-line antiretroviral therapy, prevalence of HIV drug resistance to any drug was 5%, ranging from 4.8% in 2007 to 6.8% in 2010. Most of this rise was due to an increase in the prevalence of NNRTI drug resistance, mainly in the WHO African Region.

- In the clinics surveyed, higher national coverage of antiretroviral therapy was associated with slightly greater prevalence of resistance before antiretroviral therapy initiation. Nevertheless, the overall estimated effect of an increase in antiretroviral therapy coverage on drug resistance remained modest in the areas surveyed.

Resistance at 12 months among people failing antiretroviral therapy

- In a subset of 29 surveys with 12-month follow-up data available, (i) 5.1% of the people initiating therapy – excluding those who died or who were transferred to other facilities – had drug resistance at 12 months, (ii) 76.1% achieved viral load suppression and had no acquired HIV drug resistance and (iii) 18.8% had possible drug resistance, as they were either lost to follow-up with unknown outcome, stopped treatment or had a viral load above 1000 copies/ml and no observed drug resistance.

- Of the 29 clinics that contributed 12-month follow-up data, 31% failed to achieve the WHO-recommended target of having at least 70% of people with viral load suppression at 12 months.

- Among patients alive and receiving antiretroviral therapy at 12 months, 9.4% experienced treatment failure. In a sub-set of these patients with genotype data available, 72.1% carried HIV resistant to any drug (69.5% to NNRTI, 62.5% to NRTI and 59.9% to both NNRTI and NRTI). The remaining 27.9% failing therapy did so for reasons not necessarily related to drug resistance, such as treatment interruption, and, in the absence of tests to identify HIV drug resistance, would have potentially been switched unnecessarily to costlier second-line regimens.

4.1 Overview

Acquired HIV drug resistance occurs when resistance mutations are acquired due to drug-selective pressure in individuals receiving antiretroviral therapy. Acquired HIV drug resistance may emerge because of suboptimal adherence, treatment interruption, inadequate plasma drug concentrations or the use of suboptimal drugs or drug combinations.

Some level of resistance is expected in populations on antiretroviral therapy *(1)*. In this context, monitoring drug resistance at the population level is essential to identify and implement measures to minimize the emergence of drug resistance.

4.2 Literature review on acquired drug resistance in low- and middle-income countries

The published literature was systematically reviewed to describe resistance among people failing first-line antiretroviral therapy using NNRTI-based regimens after 12 months in low- and middle-income countries. Studies were considered if resistance data at a median duration of 12 months were available for a minimum sample size of 50 people and included only individuals older than 15 years of age. Section 6 in Annex 1 provides methodological notes on the literature review protocol.

A total of nine studies from the Western Pacific and African regions were identified. Of these, four assessed patients 12 months after antiretroviral therapy initiation, 2 between 10 and 14 months of therapy initiation, one between 7 and 18 months and two between 6 and 27 months.

Table 4.1 summarizes the number of studies reporting first-line NNRTI therapy failures, by region. Most of the studies were in the WHO African Region, contributing unique data from 6 countries, and two studies were conducted in the Western Pacific Region.

Table 4.1 Number of studies included in the systematic review of acquired drug resistance, by region

	Number of studies
Africa	7
Western/Central	4
Southern	1
Eastern	2
Western Pacific	2
Total number of studies	9
Total countries represented	8
Total number of people monitored	4248
Total number of people failing with genotype	573

Table 4.2 Pooled estimates of HIV drug resistance among people experiencing first-line NNRTI therapy failure at a median duration of 12 months with genotype available, by region and by class (95% confidence levels)

	Region	Prevalence of HIV drug resistance (%) (95% CI)
Any drug class	Africa	62 (47-77)
	Western Pacific	51 (19-84)
	Overall	60 (47-72)
NRTI	Africa	57 (44-70)
	Western Pacific	46 (3-89)
	Overall	55 (42-67)
NNRTI	Africa	47 (25-69)
	Western Pacific	43 (27-59)
	Overall	46 (28-64)

A pooled analysis comprising 573 individuals with available genotypes at failure from 9 studies in 8 countries was performed and is presented in Table 4.2. Among the people for whom therapy failed at 12 months, an estimated 60% had drug resistance to any drug class (NRTI 55%, NNRTI 46%). The remaining 40% had no drug resistance, most likely due to very poor adherence and/or treatment interruption. Importantly, in the absence of tests to identify HIV drug resistance, people experiencing therapy failure without drug resistance would have been switched to second-line regimens unnecessarily.

4.3 WHO surveys to assess acquired HIV drug resistance

In addition to monitoring transmitted drug resistance, WHO recommends, as one of the key elements of its global HIV drug resistance surveillance and monitoring strategy, the surveillance of acquired HIV drug resistance in populations receiving antiretroviral therapy *(2)*. WHO prospective surveys of acquired HIV drug resistance are performed at select ART clinics and describe HIV drug resistance present before initiation of antiretroviral therapy. Additionally, surveys estimate the prevalence of viral load suppression and describe patterns of HIV drug resistance in adult and paediatric[1] populations experiencing virological failure 12 months after initiation of first-line antiretroviral therapy. At enrolment, surveys include both antiretroviral drug-naive and antiretroviral drug-exposed individuals.

1 Only Mozambique surveyed children (aged 13 years or younger).

Section 7 in Annex 1 provides methodological notes on the survey protocol.

Twelve-month survey endpoints include:

- *still receiving first-line antiretroviral therapy*;
- *switched to second-line antiretroviral therapy:* a person is classified as "switched to second-line antiretroviral therapy" if he or she changed from first- to second-line antiretroviral therapy regimen as a consequence of first-line treatment failure according to national guidelines;
- *lost to follow-up:* a person is classified as "lost to follow-up" if he or she did not return to the clinic or pharmacy for a scheduled appointment or drug pick-up for more than 90 days after the last missed clinical appointment or drug pick-up and there was no information to classify the person in one of the other endpoint categories such as death or transferred out;
- *died;*
- *stopped antiretroviral therapy:* a person is classified as having "stopped antiretroviral therapy" if he or she ceased and did not restart antiretroviral therapy at 12 months, although he or she remained in care at the site; and
- *documented transferred to another antiretroviral therapy clinic:* a person is classified as having been "transferred to another clinic" if HIV care was transferred from an HIV drug resistance survey site to any other identified treatment delivery location.

The WHO-recommended clinic level target for viral load suppression 12 months after antiretroviral therapy initiation is at least 70% (per protocol analysis, with loss to follow-up and stopping therapy treated as failure).

Importantly, clinic sampling may not have been performed in ways to ensure the representativeness of antiretroviral therapy clinics nationally or to ensure comparability over time. Therefore, national and/or regional comparisons may not be appropriate and/or applicable.

4.3.1 Overview

Between 2006 and 2010, 82 monitoring surveys were initiated in 22 countries. Data from a total of 40 surveys from 12 countries were included in this report. Thirty-six surveys had baseline data available, and 29 had 12-month endpoint information. Figure 4.1 and Table 4.3 show the geographical distribution of the WHO acquired drug resistance surveys.

Figure 4.1 Distribution of WHO surveys of acquired HIV drug resistance, by year of survey initiation, 2006–2010

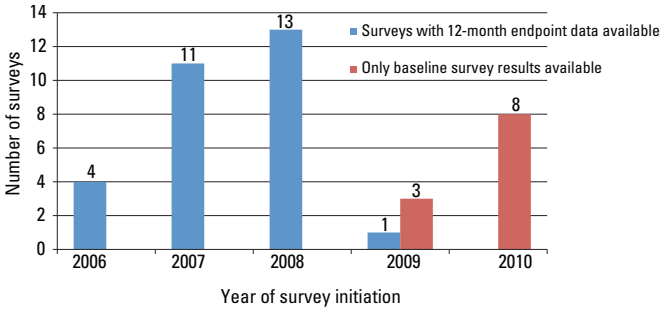


Table 4.3 Distribution of WHO surveys of acquired HIV drug resistance by location and year, 2006–2010

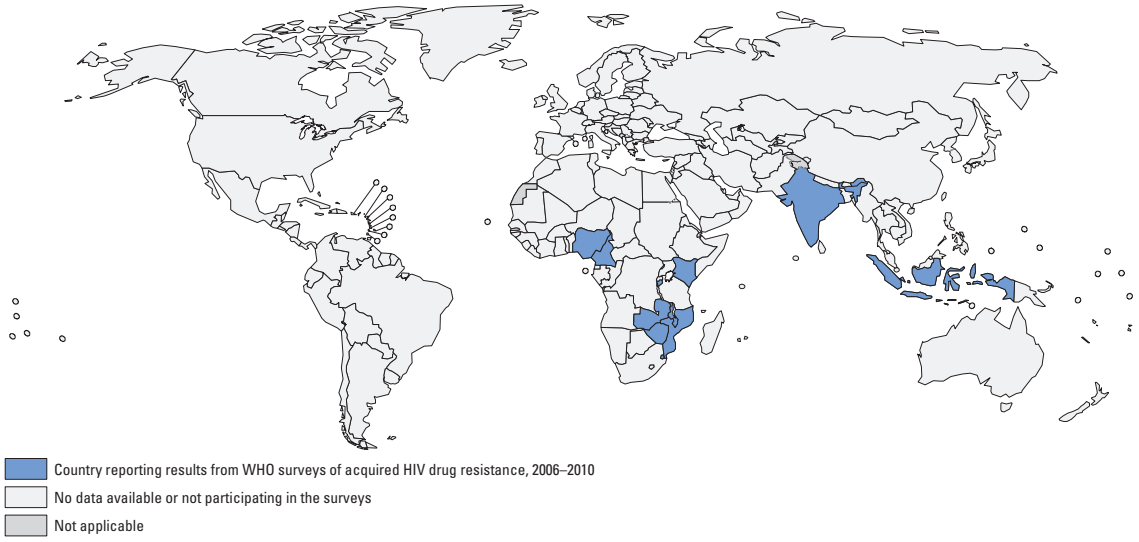
	2006	2007	2008	2009	2010	Total
African Region	4	10	11	4	8	37
Eastern Africa	4	4	5			13
Burundi		2				2
Kenya		1	1			2
Malawi	4[a]		4			8
Mozambique[b]		1				1
Western/Central			3	1		4
Cameroon				1		1
Nigeria			3			3
Southern Africa		6	3	3	8	20
South Africa		3				3
Swaziland			2			2
Zambia		3				3
Zimbabwe[c]			1	3	8	12
South-East Asia		1	2			3
India		1	1			2
Indonesia			1			1
Total	4	11	13	4	8	40

a Four surveys performed in Malawi in 2006 used a cross-sectional analysis of people receiving antiretroviral therapy for 12 months; thus baseline demographic and genotypic data are unavailable.
b Paediatric survey conducted among people aged 13 years or younger.
c Surveys initiated in Zimbabwe in 2009 (three surveys) and 2010 (eight surveys) were in progress and had only baseline genotype information available.

Overall, the vast majority (92.5%, or 37 of 40) of the surveys were conducted in the African Region (Table 4.3 and Figure 4.2).

Three countries (Cameroon, Indonesia and Mozambique) conducted the survey in only one antiretroviral therapy clinic, four countries (Burundi, India, Kenya and Swaziland) surveyed two clinics and five countries (Malawi, Nigeria, South Africa, Zambia and Zimbabwe) implemented the survey in multiple clinics.

Figure 4.2 Geographical distribution of countries (n=12) reporting results from WHO surveys of acquired HIV drug resistance, 2006–2010



Box 4.1 Improving clinic performance in Malawi

Malawi implemented WHO surveys of HIV drug resistance in four sites in 2006 and repeated them at the same four sites in 2008. Each of the four clinics was located in a different region of the country. All were large sites in urban areas, two were public sites and two were public sites receiving external technical support. The WHO target for clinic-level HIV drug resistance prevention (as measured by viral load suppression 12 months after antiretroviral therapy initiation) is 70% or higher. In 2006, both clinic 1 and clinic 2 fell short of the target, with HIV drug resistance prevention estimates of 60% and 68% respectively. In 2008, both clinics surpassed the target at 85% and 75%, respectively. The improvement in survey results was largely driven by a reduction in the prevalence of possible HIV drug resistance and, in particular, fewer people being classified as lost to follow-up 12 months after antiretroviral therapy initiation. Clinic 1 succeeded in decreasing the proportion of patients lost to follow-up by strengthening its health information systems, leading to more accurate identification of deaths and of those patients who had been transferred out to other facilities.

	Percentage of patients meeting indicated endpoint							
	2006				2008			
	Clinic 1	Clinic 2	Clinic 3	Clinic 4	Clinic 1	Clinic 2	Clinic 3	Clinic 4
HIV drug resistance prevention	60.0	67.6	79.1	83.1	85.0	74.8	73.3	83.2
Possible HIV drug resistance	37.5	27.6	18.2	13.6	9.2	20.4	24.2	10.1
HIV drug resistance detected	2.5	4.8	2.7	3.4	5.8	4.9	2.5	6.7
Lost to follow-up	16.2	19.6	13.8	4.4	5.9	13.3	17.3	8.0
Death	11.5	8.4	11.7	11.3	10.5	8.0	6.7	7.3
Stop	3.4	0	0	0	0	0	0	0

WHO recommends that surveys be repeated at the same select clinics at regular intervals to monitor programme performance. Whereas Kenya, South Africa and Zimbabwe implemented surveys in multiple years at different clinics, only Malawi surveyed the same clinics twice: four sites in 2006 and again in 2008 (Box 4.1). In Malawi, survey results and complementary operational research findings have been used to strengthen health information systems, leading to more accurate identification of deaths and those patients transferred to other facilities.

Most surveys (77.5%, or 31 of 40) were performed in urban areas, whereas 17.5% (7 of 40) and 2% (1 of 40) were implemented in rural and semiurban areas, respectively. Half of the participating clinics were public (20 of 40), 32.5% were private (13 of 40) and a minority were public with external support (17.5%, 7 of 40). Most of the surveys with available data were conducted between 2007 and 2008. This is due to the prospective nature of the survey method, which requires up to 12 months to fully enrol patients in the cohort and an additional year to reach the requisite 12-month observation endpoint. As such, most of the surveys performed in 2009 and 2010 did not have available data ready for inclusion in this report.

4.3.2 Drug resistance before initiation of first-line antiretroviral therapy (survey baseline)

In a pooled analysis of 6370 people enrolled in 40 surveys of acquired drug resistance between 2007 and 2010, 596 from 4 surveys had no baseline genotype available because no specimen was obtained; of the remaining 5774 people in 36 surveys, 680 had no baseline genotype because of PCR amplification failure.

In total, 5.0% of the people with available baseline genotypes had one or more mutations in any drug class before therapy initiation (for the definition of the mutation list, see Section 5 in Annex 1).

Of 5066 people with baseline reverse-transcriptase (RT) genotypes, 228 (4.5%) had one or more mutation associated with resistance to NRTI or NNRTI (3.7% NNRTI, 1.4% NRTI, 0.6% both NNRTI and NRTI), and 28 of 5068 with protease genotypes (0.6%) had one or more mutation associated with resistance to PI (Figure 4.4).

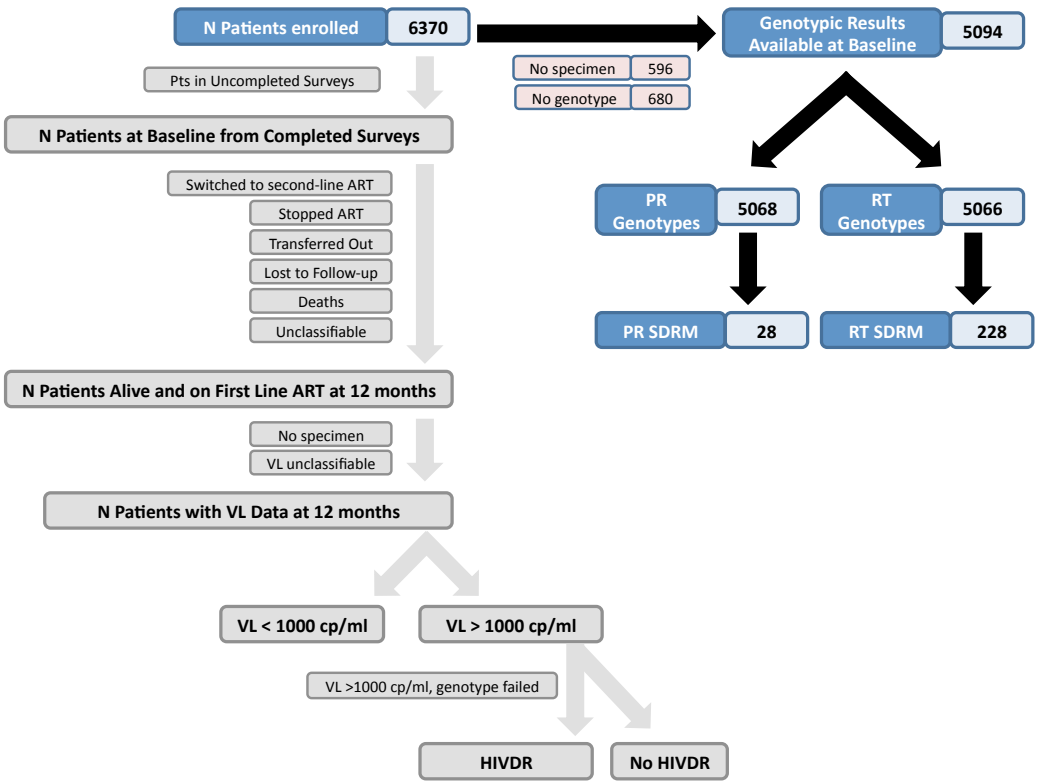
Geographically, the prevalence of NNRTI or NRTI mutations at baseline was 4.3% in surveys conducted in the WHO African Region (3.6% in the Eastern Africa subregion, 5.1% in the Southern Africa subregion and 2.5% in the Western/Central Africa subregion) and reached 6.3% in the surveys conducted in the South-East Asia Region.

Section 2 in Annex 1 summarizes methods used for sequence data analysis and quality assurance.

Figure 4.3 depicts the disposition of people in acquired drug resistance surveys from enrolment to the 12-month endpoint, focusing on survey results from people initiating first-line antiretroviral therapy.

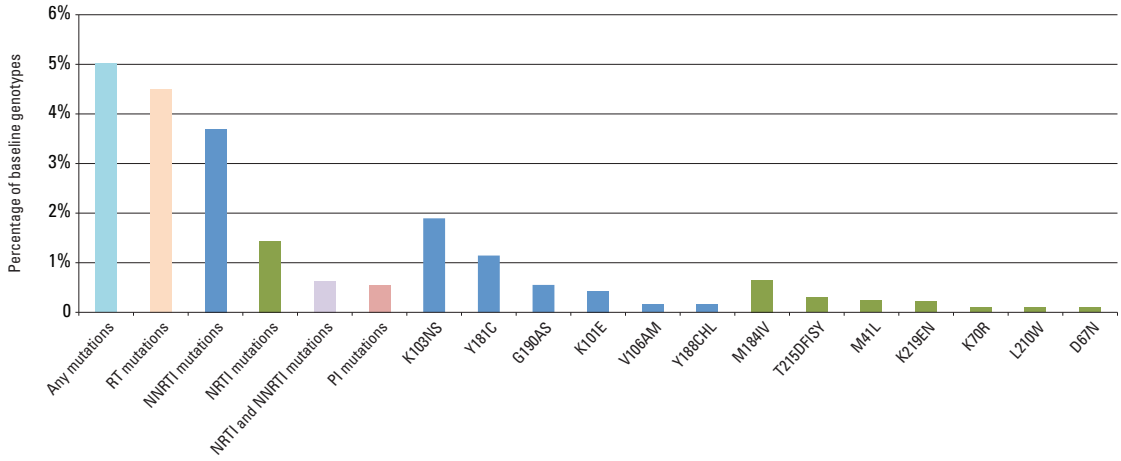
The mean prevalence of resistance mutations at baseline was 4.8% (95% CI 3.8%-6.0%) in 2007, 3.9% (95% CI 3.0%-4.9%) in 2008, 4.6% (95% CI 2.2%-7.8%) in 2009

Figure 4.3 Flow diagram of individuals enrolled in WHO surveys of acquired HIV drug resistance: from baseline to 12-month endpoints



PR: protease region of the HIV-1. RT: reverse-transcriptase region of HIV-1. SDRM: denotes the use of the 2009 WHO surveillance drug resistance mutations list in data analysis. VL: viral load. Four surveys performed in Malawi in 2006 (n = 596) used a cross-sectional analysis of people receiving antiretroviral therapy for 12 months; hence, no baseline demographic and genotype data were unavailable. Pts: Patients. N: number. Cp = copies.

Figure 4.4 Prevalence of HIV drug resistance mutation at baseline in WHO acquired HIV drug resistance surveys



Mutations were defined using the 2009 WHO surveillance drug resistance mutations list.

Table 4.4 Prevalence of HIV drug resistance at baseline in WHO acquired HIV drug resistance surveys (n=36), by year of surveys and drug class, 2007–2010

	% (95% CI)				
	2007	2008	2009	2010	P-value[a]
Any	4.8 (3.8–6.0)	3.9 (3.0–4.9)	4.6 (2.2–7.8)	6.8 (4.8–9.0)	0.06
NRTI	1.2 (0.7–2.0)	1.3 (0.8–2.0)	1.1 (0.3–2.2)	1.0 (0.3–2.1)	0.70
NNRTI	3.7 (2.5–4.9)	2.4 (1.6–3.3)	3.3 (1.8–5.1)	5.5 (3.8–7.4)	0.06
PI	0.3 (0.0–0.7)	0.4 (0.1–0.8)	0.5 (0.0–1.7)	0.0 (0.0–0.4)	0.97

a Statistical methods are described in section 9, Annex 1.

Box 4.2 Relationship between previous exposure to antiretroviral drugs and detection of resistance-associated mutations at baseline

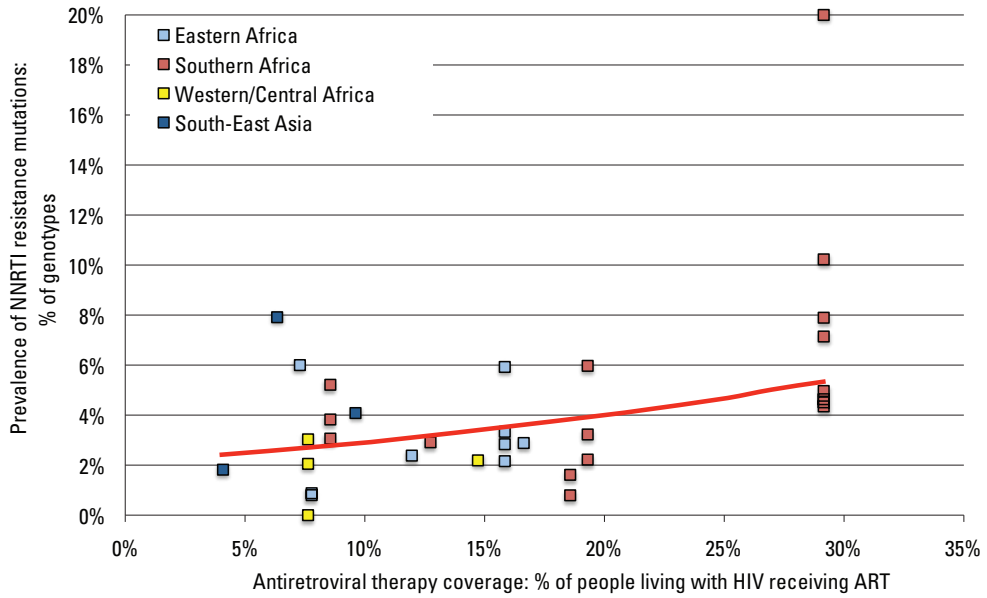
A subset of individuals enrolled in WHO surveys of acquired HIV drug resistance responded to a questionnaire about previous exposure to antiretroviral drugs for the purpose of characterizing the relationship between previous drug exposure and HIV drug resistance at baseline. Overall, 3464 people had both information about prior exposure and a RT genotype result; 286 (8.3%) reported previous antiretroviral drug exposure, 44 of whom (15.4% of the 286 reporting prior exposure) had one or more RT resistance mutations at baseline. In contrast, 3178 (89.7%) reported no previous antiretroviral drug exposure, 124 of whom (3.9% of the 3178 reporting no prior exposure) had one or more resistance mutations in RT at baseline. This suggests that people reporting prior exposure to antiretrovirals are more likely to carry HIV drug resistance at baseline (p-value < 0.001, Fisher exact test).[1]

1 Table 6 in Annex 2 details individual survey results by antiretroviral therapy clinic.

and reached 6.8% (95% CI 4.8%-9.0%) in 2010 (Table 4.4). Among the sites surveyed in the African Region, baseline NNRTI resistance rose from 3.4% (95% CI 2.4%-4.5%) to 5.4% (95% CI 3.7%-7.4%) in the same period, a statistically significant increase (p-value = 0.03), a fact that may be related to previous antiretroviral drug exposure (prevention of mother-to-child transmission, previous antiretroviral therapy) or to transmitted drug resistance. Table 5 in Annex 2 shows the estimated prevalence of baseline resistance by region and by drug class. Section 9 in Annex 1 provides additional details on the statistical methods used.

Figure 4.5 depicts the relationship between the prevalence of HIV drug resistance mutations among people initiating treatment and antiretroviral therapy coverage, defined as the number of people living with HIV receiving antiretroviral drugs divided by the total number of people living with HIV in the country where the survey was undertaken. In clinics surveyed, the prevalence of resistance mutations was positively correlated with coverage of antiretroviral therapy (p-value adjusted for region= 0.025; odds ratio per 10% ART increase 1.38, 95% CI 1.09–1.75). Nevertheless, the overall estimated effect on drug resistance of an increase in antiretroviral therapy coverage remained modest, suggesting that treatment was expanded in the areas surveyed without triggering unexpected increases in HIV drug resistance. Section 9 in Annex 1 provides additional details on the statistical methods used.

Figure 4.5 Relationship between antiretroviral therapy coverage and prevalence of NNRTI drug resistance mutations at ART initiation



Mutations were defined using the 2009 WHO surveillance drug resistance mutations list.

4.3.3 Acquired drug resistance among people failing first-line antiretroviral therapy at 12 months

Of the 6370 people enrolled, 4764 completed the survey and had endpoint data available for analysis.[1] Of these, 3475 were alive and receiving first-line antiretroviral therapy after 12 months. Seven switched to second-line regimens, 13 stopped therapy, 294 transferred care to another clinic, 599 were lost to follow-up, 362 died and 14 had unclassifiable survey endpoints (Table 4.5). Table 7 and Figure 2 in Annex 2 provide clinic-level data on the number and proportion of people lost to follow-up, stopping antiretroviral therapy, transferring out, dying and switching clinics.

WHO surveys of acquired HIV drug resistance have three survey outcomes: HIV drug resistance prevention (viral load < 1000 copies/ml), HIV drug resistance[2] and possible HIV drug resistance (included in this category are people lost to follow-up, individuals who stopped antiretroviral therapy, for whom drug resistance cannot be assessed,

Table 4.5 Endpoints of WHO acquired HIV drug resistance surveys (*n*=25) with both baseline and endpoint data available

Region	People enrolled	People on first-line ART at 12 months *n* (%)	Lost to follow-up *n* (%)	Stopped ART *n* (%)	Transferred out *n* (%)	Deaths *n* (%)	Switched to second-line ART *n* (%)	Unclassifiable *n* (%)
African Region	4365	3211 (73.6%)	541 (12.4%)	11 (0.3%)	268 (6.1%)	315 (7.2%)	7 (0.2%)	12 (0.3%)
Eastern Africa	2023	1494 (73.9%)	189 (9.3%)	6 (0.3%)	176 (8.7%)	148 (7.3%)	0 (0%)	10 (0.5%)
Southern Africa	1710	1314 (76.8%)	168 (9.8%)	5 (0.3%)	80 (4.7%)	136 (8%)	5 (0.3%)	2 (0.1%)
Western/Central Africa	632	403 (63.8%)	184 (29.1%)	0 (0%)	12 (1.9%)	31 (4.9%)	2 (0.3%)	0 (0%)
South-East Asia	399	264 (66.2%)	58 (14.5%)	2 (0.5%)	26 (6.5%)	47 (11.8%)	0 (0%)	2 (0.5%)
Overall	4764	3475 (72.9%)	599 (12.6%)	13 (0.3%)	294 (6.2%)	362 (7.6%)	7 (0.1%)	14 (0.3%)

1 Eleven surveys initiated in 2009 and 2010 in Zimbabwe with 1606 people enrolled were still ongoing as of the writing of this report, and only baseline data were available.

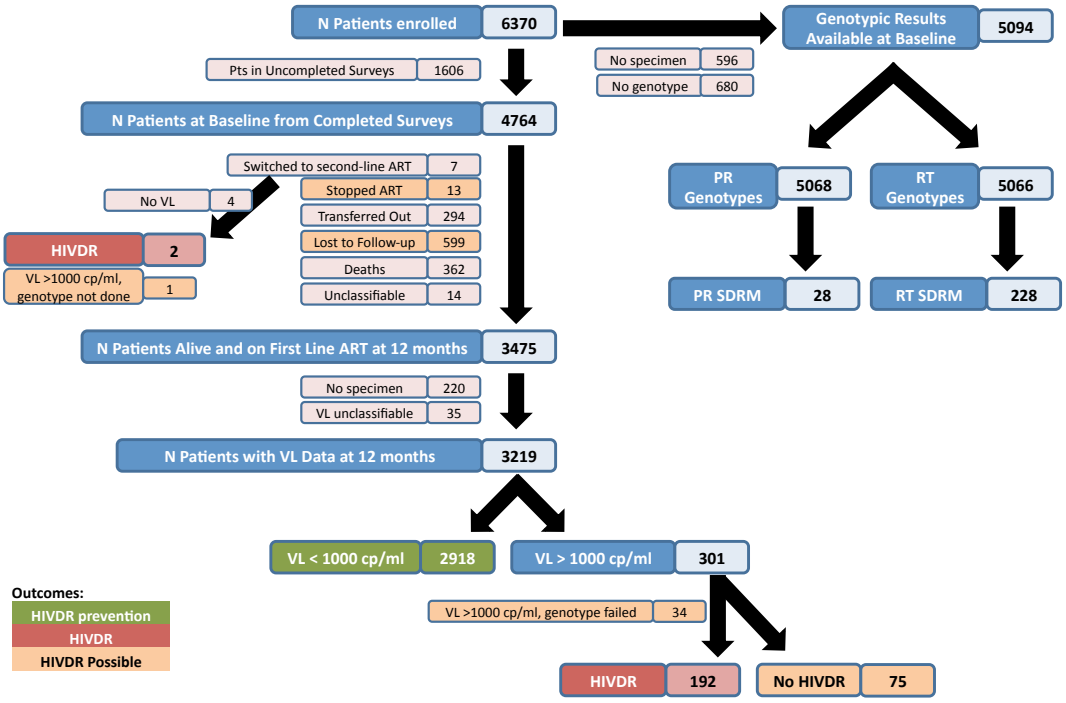
2 HIV drug resistance defined as low, moderate or high interpretation using Stanford HIV drug resistance algorithm

Table 4.6 Outcomes of the HIV drug resistance surveys at endpoints

Region	HIV drug resistance prevention (% of people initiating therapy[a])	Any HIV drug resistance at endpoint[b]		Possible HIV drug resistance (% of people initiating therapy[a])
		% of people initiating therapy[a]	% of people genotyped at treatment failure	
African Region	76.6%	4.7%	69.5%	18.8%
Eastern	79.4%	4.3%	63.7%	16.4%
Southern	80.3%	4.7%	73.3%	15.0%
Western/Central	59.9%	6.0%	74.5%	34.1%
South-East Asia	71.4%	8.9%	93.3%	19.7%
Overall	76.1%	5.1%	72.1%	18.8%

a Excludes people who died or who were transferred to another antiretroviral therapy facility.
b HIV drug resistance defined as a drug resistance prediction of low, intermediate or high level using the Stanford HIV database algorithm. Alternatively, if calculated based on the number of surveillance drug resistance mutations at endpoint, subregional, regional and overall proportions remain identical.

Figure 4.6 Flow diagram of acquired HIV drug resistance survey: 12-month endpoints and outcomes



PR: protease region of HIV-1. RT: reverse-transcriptase region of HIV-1. VL: viral load. Pts: patients. N: number. Cp: copies.

and people with viral load greater than 1000 copies/ml 12 months after therapy initiation but no drug resistance mutations detected).

Table 4.6 summarizes survey outcomes by region and subregion. Section 8 in Annex 1 provides a detailed explanation of each survey outcome and Table 8 in Annex 2 provides clinic-specific outcome results.

4.3.3.1 Drug resistance in patients failing therapy at 12 months

In total, 194 people – 5.1% of those initiating therapy, excluding patients who died or who were transferred out to other facilities – had drug resistance at 12 months.[1] Prevalence of drug resistance at 12 months varied considerably among clinics, from 0.6% in one site in South Africa (2007) to 9.7% in a clinic in India (2008).

Among those patients failing therapy, the prevalence of drug resistance was 72.1%, ranging from 25% in one clinic in Burundi (2007) to 100% in a clinic in Kenya (2008), one clinic in Nigeria (2008), one clinic in Mozambique (2007), two clinics in Malawi (one in 2006 and one in 2008) and one clinic in Indonesia (2008). This implies that almost a third of the people were failing therapy for reasons other than drug resistance. Although several factors may be at play, people with viral loads exceeding 1000 copies/ml but without drug resistance are likely to have experienced treatment interruption or have had very poor adherence. Resistance to NNRTI and NRTI was, respectively, 69.5% and 62.5% among people failing therapy with genotype data available. Table 4.7 summarizes HIV drug resistance results at survey endpoint by drug class and by region. Table 9 in Annex 2 summarizes the clinic-level results for the HIV drug resistance).

Overall, only 15% (36 of 229) of people failing ART with matching baseline-endpoint genotypes had virus with RT inhibitor resistance before antiretroviral therapy initiation. This implies that treatment failure among the remaining 85% was probably not associated with pre-existing resistance, although some may have had resistant viruses present at levels below the sensitivity of standard genotyping assays.

4.3.3.2 Drug resistance prevention

In total, 76.1% of people initiating treatment achieved viral load suppression on a standard first-line regimen at 12 months.

1 This includes two patients with HIV drug resistant virus at the time of switching to second-line therapy prior to 12 months.

Table 4.7 HIV drug resistance results among people failing therapy at 12 months, by region and drug class

Region	Number of patients	Any NRTI	Any NNRTI	NRTI and NNRTI	Any drug[a]
African Region	239	59.8%	66.9%	57.3%	69.5%
Eastern	102	52.9%	61.8%	51.0%	63.7%
Southern	90	64.4%	68.9%	60.0%	73.3%
Western/Central	47	66.0%	74.5%	66.0%	74.5%
South-East Asia	30	83.3%	90.0%	80.0%	93.3%
Overall	269	62.5%	69.5%	59.9%	72.1%

a Any drug includes NRTI, NNRTI and PI. The results for PIs are not shown. PI drug resistance was only observed for nelfinavir, resulting from the presence of multiple polymorphic mutations, especially in subtypes C, G, and CRF02_AG. Nelfinavir resistance was observed in nine specimens without NRTI or NNRTI resistance. No drug resistance was predicted for any ritonavir-boosted PI.

In the subset of people who were alive and receiving antiretroviral therapy 12 months after treatment initiation and had available viral load data, 90.6% (2918 of 3219) achieved viral load suppression. Nevertheless, at the clinic level, 31.0% (9 of 29) of sites did not achieve the WHO-suggested target of having at least 70% of people with viral load suppression 12 months after therapy initiation. Moreover, an additional 27.6% (8 of 29) of clinics clustered just above the target (70–80%). In four of the clinics, less than 60% of patients achieved viral load suppression. Poor performance leads to major consequences in term of cost and probably adversely affects morbidity and mortality outcomes. These results are particularly concerning in countries in which multiple clinics reported consistently under-performing results (Figure 4, annex 2.). Table 10 in Annex 2 summarizes the clinic-level results for the HIV drug resistance prevention outcome.

4.3.3.3 Possible drug resistance

A total of 722 (18.8%) patients were classified as having possible HIV drug resistance (75 with viral load greater than 1000 copies/ml at 12 months and no resistance, 13 who stopped antiretroviral therapy, 599 who were lost to follow-up, 34 with viral load greater than 1000 copies/ml at 12 months but with specimens failing to amplify and 1 with viral load greater than 1000 copies/ml at switch but failing to amplify PCR products).

Although only 5.1% of people initiating therapy had HIV drug resistance at 12 months, the level of possible HIV drug resistance, which factors in the unknown outcomes associated with people lost to follow-up or who stopped antiretroviral therapy, was much greater, at 18.8%. This implies that the prevalence of HIV drug resistance could be considerably higher than suggested by direct measures of HIV drug resistance.

Possible HIV drug resistance ranged widely from 4.1% in one clinic in Zimbabwe in 2008 to 46.2% in a clinic in Swaziland in 2008. Table 11 in Annex 2 summarizes clinic-level results for possible HIV drug resistance outcome.

Box 4.3 Possible HIV drug resistance: why is it important?

People categorised as having possible drug resistance are most likely to have experienced treatment interruption and/or have had very poor adherence. Treatment interruptions of NNRTI-based regimens of 48 hours or longer are associated with the selection of NNRTI drug resistance and increased risk of virological failure *(3,4)*. The fact that no HIV drug resistance was observed in 27.9% of patients failing ART at 12 months in WHO surveys may be accounted for by the fact that HIV drug resistance may have been present but predominantly reverted to drug-sensitive wild-type virus. Moreover, standard population-based sequencing (standard commercial and laboratory assays) only detects drug resistance if it is present at about 10–20% of the virus population *(5)*. Notably, HIV drug resistance present as minority variants may pass undetected, persisting for months or years after treatment *(6–8)* and may re-emerge in the viral population after treatment is reinitiated, impacting treatment outcomes adversely *(9)*.

In this analysis, high levels of possible drug resistance were mostly driven by the substantial proportions of people who were lost to follow-up or who stopped antiretroviral therapy. Figure 3 in Annex 2 provides clinic-level data on possible HIV drug resistance. WHO early warning indicator guidance recommends that no more than 20% of patients should be lost to follow-up 12 months after treatment initiation. Of the 29 surveys conducted between 2006 and 2010, 17% (5 of 29) did not meet this target. Of note, almost one third (29.1%) of the people initially enrolled in surveys conducted in the Western/Central Africa subregion were lost to follow-up at 12 months, considerably higher than the averages in other regions and subregions. The observed rates of lost to follow-up and possible drug resistance suggest the need to strengthen defaulter tracing and re-engagement mechanisms as well as health information systems. Exceptionally, at both sites surveyed in Burundi, possible HIV drug resistance was mostly caused by people with viral load greater than 1000 copies/ml and no HIV drug resistance on genotyping, suggesting patients are likely to have experienced treatment interruption or have had very poor adherence.

4.3.3.4 Prevalence and patterns of HIV drug resistance among people experiencing treatment failure 12 months after initiation

The majority (87%) of the people being treated received a thymidine analogue–containing regimen, and a relatively small proportion were on tenofovir-containing regimens (about 12%). Among the 269 individuals failing first-line antiretroviral therapy with a genotype result available, 38.7% retained susceptibility to both 3TC/FTC and tenofovir, 46.8% had a reduction in susceptibility to 3TC only and none had tenofovir resistance only. Only 14.5% had reduced susceptibility to both tenofovir and 3TC.

Correlation between regimen and HIV drug resistance outcome was not possible due to the lack of patient-level data. Thus it was not feasible to determine whether reduced susceptibility to tenofovir resulted from the use of tenofovir or stavudine among the people experiencing treatment failure.

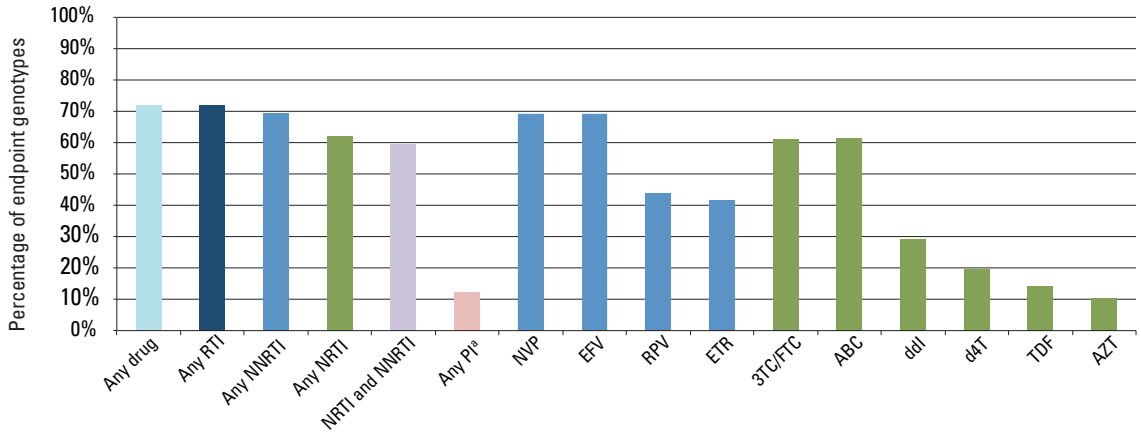
Figure 4.7 shows HIV drug resistance among patients with therapy failure 12 months after initiation, by drug and drug class. Overall, these data suggest that, if populations experiencing first-line antiretroviral therapy failure were switched to second-line regimens soon after initial virological failure, the virus would retain at least partial susceptibility to currently recommended second-line NRTI components, thus maximizing their response to boosted PI-based second-line antiretroviral therapy. This assessment is supported by the results of recent studies of the response to second-line therapy in low- and middle-income countries *(10–13)*.

Figure 4.8 shows the prevalence of HIV drug resistance mutations among people experiencing treatment failure at 12 months. Commonly observed NRTI mutations were M184V (58.7%), K65R (10.4%), D67N (7.1%), K70R (6.7%), multiple variants at T215 (5.6%) and multiple variants at K219 (4.8%).

One or more thymidine analogue resistance-associated mutations (TAM) were identified in 15.6% of the people being treated. Table 4.8 presents the distribution of endpoint genotypes (n = 269) with respect to the number of TAM detected and whether the TAM pattern resembled that seen for TAM pathways 1 or 2. One sequence had a T215ST mixture and could not be assigned to a particular pathway. TAMs are defined as: M41L, D67N, K70E or R, L210W, any mutation at T215 and any mutation at K219. Only nine of the people (3.3%) had three or more TAM, conferring high-level resistance to NRTI. Common NNRTI mutations included K101E (9.3%), K103N or S (29%), V106A or M (10.4%), Y181C, I or V (29.4%), Y188C, H or L (6.7%) and G190A or S (17.5%).

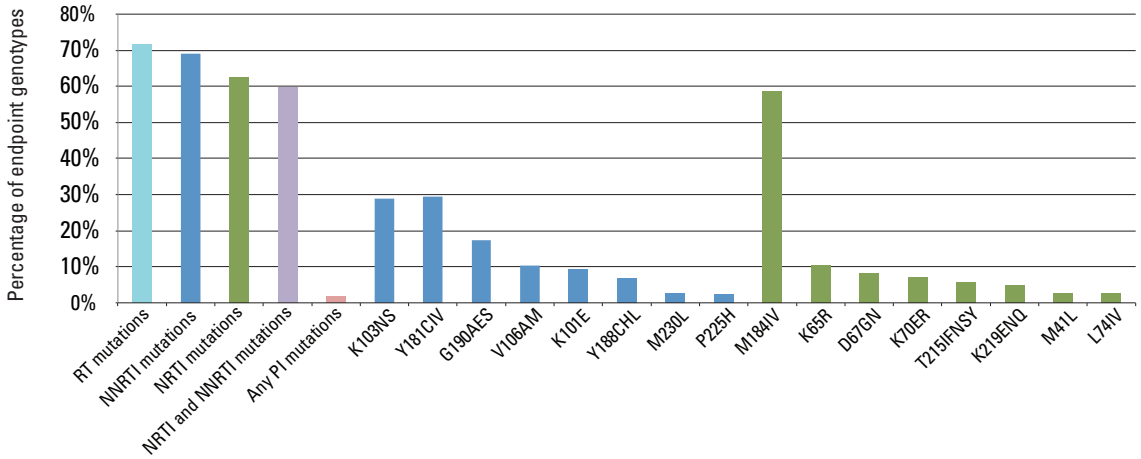
Table 12 in Annex 2 describes the distribution of HIV subtypes observed by country. Table 13 in Annex 2 provides details of drug resistance among people experiencing treatment failure at 12 months, by antiretroviral therapy clinic and geographical region. Table 14 in Annex 2 provides details about regional and site-specific prevalence of major resistance-associated mutations.

Figure 4.7 HIV drug resistance among people experiencing treatment failure at 12 months, by drug and drug class



a PI drug resistance was only observed for nelfinavir, resulting from the presence of multiple polymorphic mutations, especially in subtypes C, G and CRF02_AG. Nelfinavir resistance was never observed in specimens without predicted NRTI or NNRTI resistance. No drug resistance was predicted for any ritonavir-boosted PI. Detailed methodological note are available in Section 5, annex 1.

Figure 4.8 Prevalence of HIV drug resistance-associated mutations among people experiencing treatment failure at 12 months



Mutations were defined using the 2009 WHO surveillance drug resistance mutations list.

Table 4.8 Prevalence of thymidine analogue resistance-associated mutations (TAM), by pattern

Number of TAMs	Number of people (%)	TAM pathway 1[a] (n)	TAM pathway 2[b] (n)	TAM pathway undefined (n)
0	227 (84.6%)			
1	23 (8.2%)	3	19	1
2	10 (3.7%)	3	7	0
3	3 (1.1%)	0	3	0
4	5 (1.9%)	1	4	0
5	1 (0.4%)	0	1	0
Total	269	7	34	1

a Pathway 1 was assigned if any of the following was present: M41L, L210W or T215Y.
b Pathway 2 was assigned if any of the following were present: D67N, K70E or R, any mutation at K219 or T215F. In cases where there was overlap of TAM1 and TAM2 mutations, the amino acid at position 215 (F or Y) was used to make the determination.

REFERENCES

1. Pingen M et al. Evolutionary pathways of transmitted drug-resistant HIV-1. *Journal of Antimicrobial Chemotherapy*, 2011, 66:1467–1480.
2. Bennett DE et al. Drug resistance mutations for surveillance of transmitted HIV-1 drug-resistance: 2009 update. *PLoS One*, 2009, 4:e4724.
1. Richman DD et al. The prevalence of antiretroviral drug resistance in the United States. *AIDS*, 2004, 18:1393–1401.
2. Jordan MR et al. World Health Organization surveys to monitor HIV drug resistance prevention and associated factors in sentinel antiretroviral treatment sites. *Antiviral Therapy*, 2008, 13(Suppl. 2):15–23.
3. Parienti JJ et al. Predictors of virologic failure and resistance in HIV-infected patients treated with nevirapine- or efavirenz-based antiretroviral therapy. *Clinical Infectious Diseases*, 2004, 38:1311–1316.
4. Oyugi JH et al. Treatment interruptions predict resistance in HIV-positive individuals purchasing fixed-dose combination antiretroviral therapy in Kampala, Uganda. *AIDS*, 2007, 21:965–971.
5. Halvas EK et al. Blinded, multicenter comparison of methods to detect a drug-resistant mutant of human immunodeficiency virus type 1 at low frequency. *Journal of Clinical Microbiology*, 2006, 44:2612–2614.
6. Palmer S et al. Selection and persistence of non-nucleoside reverse transcriptase inhibitor-resistant HIV-1 in patients starting and stopping non-nucleoside therapy. *AIDS*, 2006, 20:701–710.
7. Hance AJ et al. Changes in human immunodeficiency virus type 1 populations after treatment interruption in patients failing antiretroviral therapy. *Journal of Virology*, 2001, 75:6410–6417.
8. Lecossier D et al. Detection of minority populations of HIV-1 expressing the K103N resistance mutation in patients failing nevirapine. *Journal of Acquired Immune Deficiency Syndromes*, 2005, 38:37–42.
9. Li JZ et al. Low frequency HIV-1 drug resistance mutations and risk of NNRTI-based antiretroviral treatment failure. *JAMA*, 2011, 305:1327–1335.
10. Hosseinipour MC et al. The public health approach to identify antiretroviral therapy failure: high-level nucleoside reverse transcriptase inhibitor resistance among Malawians failing first-line antiretroviral therapy. *AIDS*, 2009, 23:1127–1134.
11. Bartlett JA et al. Lopinavir/ritonavir monotherapy after virologic failure of first-line antiretroviral therapy in resource-limited settings. *AIDS*, 2012, [Epub ahead of print].
12. Hosseinipour MC et al. Second-line treatment in the Malawi antiretroviral programme: high early mortality, but good outcomes in survivors, despite extensive drug resistance at baseline. *HIV Medicine*, 2010, 11:510–518.
13. Sigaloff KCE et al. Second-line antiretroviral treatment successfully re-suppresses drug-resistant HIV-1 after first-line failure: prospective cohort in sub-Saharan Africa. *Journal of Infectious Diseases*, 2012, 205:1739–1744.

5. EARLY WARNING INDICATORS

KEY MESSAGES

- Early warning indicators of HIV drug resistance monitor factors at individual clinics known to create situations favourable to the emergence of HIV drug resistance. The timely identification of clinics with suboptimal performance helps to target appropriate interventions that can potentially reduce the risk of HIV drug resistance emerging and optimize care. Since 2004, early warning indicators have been monitored at 2017 antiretroviral therapy clinics in 50 countries assessing 131 686 people.
- Overall, 75% of clinics monitored met the target of 100% of patients receiving prescriptions for antiretroviral therapy in accordance with national or WHO guidelines. Whereas 74% of clinics surveyed in Africa and 80% in Asia met this target, only 46% achieved it in Latin America and Caribbean.
- With respect to patients lost to follow-up at 12 months (early warning indicator 2), overall 69% of clinics monitored met the WHO-recommended target, ranging from 59% in Africa to 75% in Asia and 85% in Latin America and the Caribbean. Sixty-seven per cent of clinics met the recommended level for retention on first-line antiretroviral therapy at 12 months (early warning indicator 3).
- Seventeen per cent of reporting clinics achieved WHO's recommended target for on-time drug pick-up (early warning indicator 4), and 58% met WHO's recommended target for on-time appointment keeping (early warning indicator assessing 5). With respect to drug supply continuity (early warning indicator 6), only 65% of reporting clinics provided a continuous supply of antiretroviral drug during a 12-month period.
- Although the small number of reporting sites precludes regional or global generalizations, reported data identified important gaps in service delivery and programme performance, particularly in procurement and supply systems, patient adherence and clinic retention.

5.1 Overview[1]

In the face of slowly increasing drug resistance trends, and the growing use of antiretroviral therapy for both treatment and prevention, efforts must be redoubled to ensure that the emergence of drug resistance is adequately monitored and minimized. Several antiretroviral treatment programme and site factors have been shown (see Chapter 1) to be closely associated with the emergence and transmission of HIV drug resistance, including the quality of care, adherence to antiretroviral therapy and clinic and programme functioning *(1,2)*.

Whereas genotyping is expensive and complex, the monitoring of such factors is comparatively inexpensive and can be successfully used to timely identify gaps in service delivery so that corrective action can be taken to minimize the emergence of HIV drug resistance. In 2004, WHO developed a set of eight HIV drug resistance early warning indicators to monitor these factors, each associated with a recommended target for clinic-level monitoring.

Since 2004, more than 50 countries have monitored one or more early warning indicators at select clinics. Although WHO recommends that early warning indicators be monitored annually at all antiretroviral therapy clinics within a country or at a large number of representative clinics, most countries have monitored early warning indicators in a convenient sample of sites. Therefore, the data obtained are not nationally representative and preclude the assessment of regional/global trends. Nevertheless, reports documented important gaps in service delivery and programme performance.

Table 5.1 summarizes the results from cohorts of people initiating antiretroviral therapy between 2004 and 2009, assessing 131 686 people at 2107 clinics since 2004,

1 This section relies extensively on Bennett et al *(4)*.

comprising: African Region, 907 clinics in 25 countries; Asia (Western Pacific Region and South-East Asia Region combined): 1048 clinics in 6 countries; Latin America and the Caribbean: 148 clinics in 18 countries; and European Region: 4 clinics in 1 country.

Early warning indicators 1, 2 and 3 (prescribing practices, loss to follow-up and retention on first-line antiretroviral therapy at 12 months, respectively) were the three indicators most frequently monitored. Despite their important relationship to HIV drug resistance, a minority of clinics reported early warning indicators 4 and 5, and the reporting of early warning indicator 6 was intermediate. The frequency with which early warning indicators 1–6 were reported was probably associated with the ease of data abstraction. Early warning indicator 7 (adherence assessed through pill count; rarely implemented in programme practice) was monitored in only two countries (less than 1% of clinics) and was excluded from the analysis. Very few clinics reported on early warning indicator 8 because of limited routine use of viral load testing for clinical monitoring purposes. In the future, as viral load testing becomes more accessible, reporting of rates of viral load suppression is anticipated to increase.

The percentage of adult clinics meeting WHO-recommended targets varied considerably by early warning indicator and region (Table 5.1).

Available data indicate that, overall, 75% of clinics monitored met the target of 100% of the service users receiving prescriptions for antiretroviral therapy in accordance with national or WHO guidelines (early warning indicator 1). Whereas 74% and 80% of clinics in Africa and Asia, respectively, met this target, only 46% achieved it in Latin America and the Caribbean. This may be related to the greater use of more individualized approaches to antiretroviral therapy in Latin America and the Caribbean and the classification of first-line regimens that contained PI or tenofovir as "inappropriate" when not recommended by national guidelines, even though they would not unduly have selected for HIV drug resistance.

With respect to early warning indicator 2 (loss to follow-up at 12 months), 69% of clinics met the WHO-recommended target, ranging from 59% in the African Region to 75% in Asia and 85% in Latin America and the Caribbean. No direct comparisons can be made since the countries and clinics surveyed were not the same, but this result is broadly consistent with the relatively higher levels of loss to follow-up observed in some of the sites monitored in the African Region in the context of surveys of acquired drug resistance (Chapter 4).

Sixty-seven per cent of the clinics met the recommended level for early warning indicator 3 (retention on first-line antiretroviral therapy), with regional averages ranging

Table 5.1 Number of clinics monitored and percentage of clinics achieving recommended targets by early warning indicator and region by adult cohorts, 2004–2009

Indicator		**Early warning indicator 1:** Prescribing practices	**Early warning indicator 2:** Loss to follow-up	**Early warning indicator 3:** Retention on first-line antiretroviral therapy at 12 months	**Early warning indicator 4:** On-time antiretroviral drug pick-up	**Early warning indicator 5:** On-time appointment keeping	**Early warning indicator 6:** Antiretroviral drug supply continuity	**Early warning indicator 8:** Viral load suppression at 12 months
Target		100%	≤20%	≥70%	≥90%	≥80%	100%	≥70%
African Region (all years)	Number of clinics	907	794	863	321	309	537	24
	% of clinics meeting recommended level	74%	59%	61%	15%	43%	63%	96%
Asia (all years)	Number of clinics	1048	1043	1045	10	1037	100	—
	% of clinics meeting recommended level	80%	75%	72%	0%	64%	89%	—
Latin America and the Caribbean (all years)	Number of clinics	141	116	132	21	20	86	22
	% of clinics meeting recommended level	46%	85%	71%	57%	15%	51%	73%
Total (all regions, all years)	Number of clinics	2096	1953	2040	352	1366	723	46
	% of clinics meeting recommended level	75%	68%	67%	17%	57%	65%	85%

The sites surveyed reflect health systems that are highly heterogeneous in structure and funding, and such differences may have influenced early warning indicator findings. In addition, country-specific data heavily influenced regional and global data; for example, Thailand monitored a considerably larger number of clinics than any other country (902 of 2107 adult clinics included in the analysis and 296 of 331 paediatric clinics). Moreover, clinic sampling may not have been performed in ways to ensure the representativeness of antiretroviral therapy clinics nationally. National and/or regional comparisons may therefore not always be appropriate or applicable.
Early warning indicator 7 (adherence assessed through pill count) was excluded from the analysis since it was monitored in only two countries (less than 1% of clinics).
— Data not available or applicable.

between 60% and 70%. Improving retention on first-line antiretroviral therapy at 12 months is essential, since many countries and clinics have only one second-line regimen available and no salvage alternatives. Thus, it is necessary to optimize adherence to first-line antiretroviral therapy and minimize inappropriate switching to second-line regimens during the first 12 months to enhance the long-term success of population-based antiretroviral therapy.

Although few clinics monitored viral load suppression at 12 months, among those that did, 85% met the WHO-recommended target.

Seventeen per cent of reporting clinics achieved WHO's recommended level for early warning indicator 4 (on-time drug pick-up), and 58% achieved WHO's recommended target for early warning indicator 5 (on-time appointment keeping). With respect to early warning indicator 6, only 65% of reporting clinics provided a continuous supply of antiretroviral drugs during a 12-month period, ranging from 51% to 89% in different regions. Although the small number of reporting sites precludes generalizing these rates to specific regions, available data indicate that procurement and supply distribution remain as important programme challenges.

5.2 Revised early warning targets and indicators

In 2012, after a critical review of the available medical literature and the multiple challenges observed with data collection and reporting, early warning indicators were simplified and harmonized with other monitoring and evaluation frameworks and processes, including those of the United Nations Special Session on HIV/AIDS and the United States President's Emergency Plan for AIDS Relief.

The number of core indicators (Table 5.2) has been reduced to four: on-time pill pick-up, dispensing practices, drug supply continuity and clinic retention at 12 months. A fifth indicator, viral load suppression at 12 months, is recommended and should be monitored at sites where viral load testing is routinely performed 12 months after therapy initiation.

The revised set of indicators is anticipated to require less data abstraction, facilitating wider uptake and reporting.

Recommended targets have been adjusted to take into account new scientific evidence on optimal programme management and performance. Monitoring of early warning indicators is now based on a scorecard approach (Table 5.2) to facilitate the interpretation of programme data. Scorecards produce three classifications: red (poor performance, below the desired level), amber (fair performance, not yet at the desired level) and green (excellent performance, achieving the desired level). Scorecarding also allows for a grey classification if clinics do not monitor a specific early warning indicator and a white classification if an indicator is not reported in a specific year following predetermined national convention *(3)*.

Early warning indicators provide crucial information on the performance of treatment clinics and can be instrumental in prioritizing actions and allocating resources for clinics most in need. Aggregating early warning indicator results from a representative sample or all clinics within a country can highlight broader programmatic issues hampering the achievement of desired outcomes so that treatment outcomes can be maximized and the emergence of HIV drug resistance can be minimized.

Table 5.2 Revised set of early warning indicators and WHO-recommended targets (2012)

HIV drug resistance early warning indicator scorecard		
Early warning indicator	Status	Target
1. On-time pill pick-up	Red/ amber/ green	Red: <80% Amber: 80–90% Green: >90%
2. Retention in care[a]	Red/ amber/ green/ white	Red: <75% retained after 12 months of antiretroviral therapy Amber: 75–85% retained after 12 months of antiretroviral therapy Green: >85% retained after 12 months of antiretroviral therapy
3. Pharmacy stock-outs	Red/ green	Red: <100% of a 12-month period with no stock-outs Green: 100% of a 12-month period with no stock-outs
4. Dispensing practices	Red/ green	Red: >0% dispensing of mono- or dual therapy Green: 0% dispensing of mono- or dual therapy
5. Viral load suppression[b]	Red/ amber/ green	Red: <70% viral load suppression after 12 months of antiretroviral therapy Amber: 70–85% viral load suppression after 12 months of antiretroviral therapy Green: >85% viral load suppression after 12 months of antiretroviral therapy

Red: poor performance, below the desired level.
Amber: fair performance, not yet at the desired level but progressing towards the desired level.
Green: excellent performance, achieving the desired level.
Grey: data not available.
White: retention indicator not reported in a specific year following a predetermined national convention.

a Retention indicator is identical to the following indicators: UNGASS no. 24; United States Presidents' Emergency Plan for AIDS Relief no. T1.3.D; and Global Fund to Fight AIDS, Tuberculosis and Malaria impact no. HIV-I3 retention indicator (which is only monitored and reported biannually).

b The targets for viral suppression for children <2 years old have been modified as follows:
Red: <60% viral load suppression after 12 months of antiretroviral therapy.
Amber: 60–70% viral load suppression after 12 months of antiretroviral therapy.
Green: >70% viral load suppression after 12 months of antiretroviral therapy.

REFERENCES

1. Bennett DE et al. The World Health Organization's global strategy for prevention and assessment of HIV drug resistance. *Antiviral Therapy*, 2008, 13(Suppl. 2):1–13.
2. Jordan MR. Assessments of HIV drug resistance mutations in resource-limited settings. *Clinical Infectious Diseases*, 2011, 52:1058–1060.
3. HIV drug resistance [web site]. Geneva, World Health Organization, 2012 (http://www.who.int/hiv/drugresistance, accessed 28 June 2012).
4. Bennett DE et al. HIV Drug Resistance Early Warning Indicators in Cohorts of Individuals Starting Antiretroviral Therapy between 2004 and 2009: World Health Organization Global Report from 50 Countries. *Clinical Infectious Diseases*, 2012:54 (Suppl 4). S280-S289.

6. CONCLUSIONS

In December 2003, less than 400 000 people received antiretroviral therapy in low- and middle-income countries, representing less than 7% of the estimated number of people in need. Communities were being ravaged by the epidemic, life expectancy was falling precipitously in many countries and the economic and social gains achieved over the previous decades were being reversed. Given these circumstances, rapidly expanding access to antiretroviral therapy was not only an ethical imperative towards those affected but had also become a global security need. Nevertheless, despite the urgent need for action, concern existed about how delivering a lifelong intervention in settings with limited resources and infrastructure might affect the emergence and transmission of drug-resistant HIV.

Since 2003, coverage of antiretroviral therapy has grown dramatically and, as of December 2011, more than 8 million people were receiving antiretroviral therapy in low- and middle-income countries. Based on data from published studies and on the results of surveys conducted following standardized WHO methods, this report reveals three major conclusions. First, with the expansion of treatment achieved over the last eight years, there are signals of increasing prevalence of transmitted HIV drug resistance among recently-infected populations in the areas surveyed, particularly to NNRTI. However, though increasing, transmitted HIV drug resistance has not occurred at the high levels some had predicted as a consequence of the rapid scale-up of antiretroviral therapy. As such, currently-recommended first-line regimens should lead to viral suppression for most individuals initiating antiretroviral therapy.

Second, with respect to acquired drug resistance, WHO surveys indicate that, if people are switched to second-line regimens soon after virological failure, standard second-line treatment combinations are likely to be effective for the majority of patients failing first-line therapy.

Third, drug resistance surveillance provides important information on the effectiveness of ART programmes and services. Monitoring of ART programme functioning through WHO HIV drug resistance early warning indicators in 50 countries has highlighted the existence of important gaps in service delivery and programme performance, particularly with respect to procurement and supply systems, adherence and clinic retention.

The results presented in this report are not intended to be representative of the countries from which they were reported and should not be generalized beyond the populations surveyed. However, findings should be interpreted as an alert to programme managers that resistance transmission and acquisition are occurring and that wider policy action may be warranted.

Transmitted drug resistance

Overall, transmitted resistance is estimated to have increased in the areas and populations surveyed, and this pattern appears to have been driven by increased resistance to the NNRTI class. An increase in transmitted drug resistance was particularly apparent in some of the areas surveyed in the African Region, a fact that may be partly explained by the relative abundance of data from these areas. Such an increase in transmitted resistance is not unexpected and probably reflects the considerable progress achieved by many low- and middle-income countries in expanding access to antiretroviral drugs.

Available HIV drug resistance data suggest that currently recommended first-line antiretroviral therapy regimens are effective for most people initiating treatment. As antiretroviral therapy continues to be rolled out, however, increased rates of transmitted drug resistance may occur, and robust surveillance systems must be in place to detect potential future increases in a timely manner. Moreover, focused efforts are needed to identify levels and trends among specific populations at higher risk of HIV infection, such as men who have sex with men, people who inject drugs and sex workers, among whom HIV prevalence tends to be considerably greater than background levels.

Reports from surveys showing moderate levels of transmitted resistance deserve particular attention. Surveillance of transmitted resistance should be repeated in these areas to confirm the results and be expanded to additional regions. In addition, antiretroviral therapy clinic and programme factors in areas reporting moderate levels of transmitted drug resistance should be investigated to assess their potential contributions to the emergence and transmission of drug-resistant HIV.

If levels higher than 15% of transmitted drug resistance are detected, it is recommended that full-scale national surveillance of HIV drug resistance in populations initiating

antiretroviral therapy be performed immediately to identify any changes needed to ensure the effectiveness of first-line antiretroviral therapy. Moreover, an analysis of drug resistance among women living with HIV should be conducted to inform the selection of regimens for preventing mother-to-child transmission. These surveys should provide a point prevalence estimate of HIV drug resistance and trigger public health action based on cost–effectiveness thresholds. Importantly, at present no changes to current treatment or prophylactic guidelines are warranted based on the data presented.

Acquired drug resistance

Data from published studies and WHO surveys in low- and middle-income countries indicate that, after 12 months of antiretroviral therapy, between 82% and 91% of the people assessed achieved viral load suppression (treatment success). Among those experiencing therapy failure, between 60% and 70% had drug resistance, implying that the remaining 30%–40% experienced therapy failure for other reasons, such as very low adherence or long treatment interruptions, and, in the absence of HIV drug resistance testing, could potentially have been switched to costlier second-line regimens unnecessarily. Notably, of the 304 people in WHO surveys failing therapy in the first 12 months after treatment initiation, only 7 switched to second-line antiretroviral therapy. This may be due to the limited ability to detect early failure using clinical or immunological means or difficulty in accessing second-line treatment. It also illustrates the potential of routine viral load monitoring.

In the areas assessed by WHO surveys, the prevalence of HIV drug resistance in populations initiating antiretroviral therapy was relatively low (5%). The resistance profile of the people experiencing treatment failure at 12 months suggests that, if they were switched to second-line therapy at this specific time, most would likely respond to currently recommended, boosted PI-based second-line antiretroviral regimens.

At 18.8%, the prevalence of possible HIV drug resistance observed in WHO surveys is concerning and merits attention. Although the causes of possible HIV drug resistance varied from clinic to clinic, they were generally associated with high rates of loss to follow-up observed in some of the sites surveyed, especially in Western/Central Africa, suggesting the need to strengthen mechanisms to trace and re-engage defaulters in care.

Poor retention rates in many clinics are also concerning. Given the relationship between treatment interruption and HIV drug resistance, observed retention rates are concerning, especially as antiretroviral therapy continues to be scaled up, and clinics will face the double challenge of successfully managing a growing number of patients for longer.

Early warning indicators

Monitoring of HIV drug resistance early warning indicators is an important component of global and national strategies to minimize the emergence of preventable HIV drug resistance. Monitoring early warning indicators can identify weaknesses at the antiretroviral therapy clinic and programme levels that may result in suboptimal treatment or treatment interruption, potentially causing HIV drug resistance to emerge. Early warning indicators analyse routinely collected data through a drug resistance lens. As such, they are the first line in preventing HIV drug resistance.

Monitoring early warning indicators also identifies successful clinics that could serve as best practice models for other clinics. Between 2004 and 2009, 50 countries monitored one or more early warning indicators at select clinics. Although no global trends or conclusions can be assessed, such experiences have shown that important gaps in service delivery and programme performance affect a considerable proportion of clinics delivering antiretroviral therapy, particularly with respect to the fragility of procurement and supply systems and inadequate adherence and clinic retention.

Given the limited number of antiretroviral drugs available in many low- and middle-income countries, including the absence of third-line or salvage regimens, and the cost and toxicity of second-line drugs, the duration of time on effective fully suppressive first-line antiretroviral therapy regimens must be maximized. Moreover, as viral load monitoring and individual HIV drug resistance genotyping are often unavailable, successful antiretroviral therapy programmes should strive to exceed recommended targets assessed though early warning indicator monitoring.

In addition, as increasing numbers of people are placed on second-line antiretroviral therapy, developing strategies for surveillance of drug resistance to second-line and salvage regimens may be necessary.

WHO recommends that surveys be repeated regularly to detect signals of increasing transmission of resistance and to assess the improvement of programmes in minimizing the emergence of acquired resistance. However, few countries have repeated surveys, and many have never engaged in surveillance activities. It is essential that HIV drug resistance surveillance activities be perceived and integrated as critical components of the monitoring and evaluation framework of treatment programmes. In addition, while cost may be perceived as a barrier, HIV drug resistance surveillance activities represent only a small fraction of the global investment in the HIV response.

Robust programme monitoring, including surveillance of transmitted and acquired HIV drug resistance, is vital to ensure that a decade of declining HIV-related morbidity and mortality is not reversed. WHO, through its partner network of collaborating institutions, is committed to monitoring HIV drug resistance globally and to advocate for scaling up routine surveillance using standardized methods and increased mobilization of national and international funds to support HIV drug resistance surveillance.

ANNEX 1. METHODOLOGICAL NOTES

Section 1. Regional and subregional country groupings[1]

Central Africa:
Cameroon; Central African Republic; Chad; Congo; Democratic Republic of the Congo; Equatorial Guinea; Gabon; Sao Tome and Principe

Eastern Africa:
Burundi; Comoros; Djibouti; Eritrea; Ethiopia; Kenya; Madagascar; Malawi; Mauritius; Mozambique; Rwanda; Seychelles; Somalia; Sudan; Uganda; United Republic of Tanzania

Southern Africa:
Angola; Botswana; Lesotho; Namibia; South Africa; Swaziland; Zambia; Zimbabwe

Western Africa:
Benin; Burkina Faso; Cape Verde; Côte d'Ivoire; Gambia; Ghana; Guinea; Guinea-Bissau; Liberia; Mali; Mauritania; Niger; Nigeria; Senegal; Sierra Leone; Togo

South-East Asia:
Bangladesh; Bhutan; Democratic People's Republic of Korea; India; Indonesia; Maldives; Myanmar; Nepal; Sri Lanka; Thailand; Timor-Leste

Western Pacific:
Australia; Brunei Darussalam; Cambodia; China; Cook Islands; Fiji; Japan; Kiribati; Lao People's Democratic Republic; Malaysia; Marshall Islands; Micronesia (Federated States of); Mongolia; Nauru; New Zealand; Niue; Palau; Papua New Guinea; Philippines; Republic of Korea; Samoa; Singapore; Solomon Islands; Tonga; Tuvalu; Vanuatu; Viet Nam

Section 2. WHO Sequence data analysis and quality assurance for surveys to assess transmitted and acquired drug resistance

Genotyping of protease (PR) and reverse transcriptase (RT) was performed in laboratories within the WHO Laboratory Network, mostly using in-house methods based on RT-PCR of RNA extracted from plasma or dried blood spots, followed by standard bulk sequencing techniques. In some cases, commercial kits (TruGene or ViroSeq) were used. Member laboratories undergo an intensive inspection and review process and participate in annual external proficiency testing *(1)*.

Nucleotide sequences were analysed using the Calibrated Population Resistance (CPR, version 5) program on the Stanford HIV Database web site (http://cpr-v.stanford.edu/cpr/servlet/CPR), and the following parameters and thresholds were used for sequence rejection: (1) amino acid sequence identical to the subtype B consensus, i.e. most likely a lab strain contaminant; (2) any insertions not near PR amino acid position 38 or RT amino acid position 69; (3) any deletions not near RT position 69, at the last codon sequenced in RT or past RT position 300; (3) any stop codons not present as mixtures unless located after RT position 300; (4) any frameshifts resulting in more than three consecutive mutations; (5) more than 20 atypical mutations; (6) missing PR sequence between position 46 and 90 or between RT position 41 and 190; and (7) more than two ambiguous amino acids (X's) in PR or RT before position 300 or any at a drug resistance mutation site.

Analysis was performed using MEGA 5.05 (http://www.megasoftware.net) by constructing neighbour-joining trees and genetic distance matrices from trimmed sequences (PR positions 1-99 and RT positions 1-250) with 1000 bootstrap iterations and missing data and gaps handled by pairwise deletion. For surveys of transmitted drug resistance, where it is not expected to observe two highly related sequences, one member of any pair with genetic distance of 0 or 1 (that is, 0 or only 1 nucleotide

1 Subregional country grouping for Africa is available at www.unicef.org/wcaro/WCARO_SOAC08_Fig011.pdf (accessed 11 July 2012).

difference between the 2 PR-RT sequences) was rejected. For surveys of acquired DR, expected baseline-endpoint pairs (based on patient ID codes) were confirmed, or if found not to cluster on the neighbour-joining tree, were rejected. In some cases, sequences were relabelled when phylogenetic analysis indicated that a specimen had been mislabelled.

Section 3. Methods of the literature review on drug resistance in ARV-naive recently- or chronically-infected populations in low- and middle-income countries

English-language articles from PubMed, EMBASE and major conference abstracts were searched for the period 1 January 2003 to 31 July 2011. Studies were considered if they included untreated recently or chronically infected individuals older than 15 years and had more than 10 specimens successfully genotyped. The geographical focus was limited to low- and middle-income countries from Asia, sub-Saharan Africa (eastern, southern, western/central) and Latin America and the Caribbean. Studies were excluded if they only reported resistance in the context of preventing mother-to-child transmission or used sequencing methods other than standard bulk sequencing, such as genome sequencing, allele-specific PCR and ultra-deep sequencing.

WHO transmitted HIV drug resistance survey results published by country authors were excluded from this review. Individuals who were newly diagnosed at health facilities or those eligible to initiate antiretroviral therapy were classified as chronically infected. Recently infected individuals were defined through epidemiological surrogate criteria for recent infection, through serial antibody testing or through a detuned antibody algorithm.

The studies were assessed according to mid-point year of recruitment and by region. Heterogeneity between studies was examined by pooling studies using random-effects meta-analyses and assessing the I^2 statistic. Owing to the fact that the proportion of individuals with a drug resistance mutation was very low, we were unable to use the standard normal approximation to the binomial distribution to perform these meta-analyses. Instead, we transformed the individual studies using a Freeman-Tukey–type arcsine square root transformation: $y=\arcsin[\sqrt{(r/(n+1)}] + \arcsin[\sqrt{(r+1)/(n+1)}]$, with a variance of $1/(n+1)$; where r is the number of individuals with a mutation, and n is the number of individuals genotyped.

The I^2 statistic was assessed on these transformed proportions before back transformation for estimation of pooled prevalences. Pooled estimates of the prevalence of drug class-specific mutations (NRTI, NNRTI and PI) by region and over time were calculated. Statistical analysis was performed in Stata version 11.2 (StataCorp, USA).

Meta-regressions were performed by using mixed logistic regression models. Specifically these models included a fixed effect to account for differences between WHO regions and random effects at the study level to account for between-study heterogeneity within region.

Many of the studies included in this meta-analysis were performed using distinct methods and may differ with respect to the population studied (such as recent or chronic infections), the sampling frame (such as consecutive, convenient, or random selection from general population) and the laboratory methods used (such as dried blood spots or plasma samples or genotyping methods used). Individual studies may also have been influenced by regional factors such as antiretroviral therapy coverage and availability, variation in HIV subtypes, quality of care at the individual sites and antiretroviral therapy programmes, country income levels and the structure or organization of health services. As such, prevalence estimates may not be nationally or regionally representative.

Moreover, studies reported resistance data according to any of the internationally recognized lists, and variations in how mutations are defined may have influenced individual study results and, hence, aggregate analyses. This may particularly be the case for estimates of PI resistance. Stratification of the dataset by classes and regions may have reduced the statistical power to detect region-specific trends over time.

For the purpose of the analysis, each study providing data for both chronic and recently infected individuals was considered as two separate studies.

Table 1. Studies included in the literature review of HIV drug resistance among ARV-naive recently- or chronically-infected populations

Study	Region	Country	Mid-point year of recruitment
de Madeiros et al.	Latin America	Brazil	2003
Cardoso et al.	Latin America	Brazil	2003
Vergne et al.	Western/Central Africa	Burkina Faso	2003
Vessiere et al.	Western/Central Africa	Cameroon	2003
Perez et al.	Latin America	Cuba	2003
Kassau et al.	Eastern Africa	Ethiopia	2003
Lloyd et al.	Latin America	Honduras	2003
Balakrishnan et al.	South-East Asia	India	2003
Deshpande et al.	South-East Asia	India	2003
Escoto-Delgadillo et al.	Latin America	Mexico	2003
Bartolo et al.	Eastern Africa	Mozambique	2003
Bellocchi et al.	Eastern Africa	Mozambique	2003
Perreira et al.	Eastern Africa	Mozambique	2003
Lama et al.	Latin America	Peru	2003
Lama et al.	Latin America	Peru	2003
Bessong et al.	Southern Africa	South Africa	2003
Jacobs et al.	Southern Africa	South Africa	2003
Chonwattana et al.	South-East Asia	Thailand	2003
Galluzzo et al.	Eastern Africa	Uganda	2003
Bouchard et al.	Latin America	Venezuela	2003
Ferreira da Silva et al.	Southern Africa	Angola	2004
Dilernia et al.	Latin America	Argentina	2004
Dilernia et al.	Latin America	Argentina	2004
Gonsalez et al.	Latin America	Brazil	2004
Rodrigues et al	Latin America	Brazil	2004
Ly et al.	Western Pacific	Cambodia	2004
Soares et al.	Western/Central Africa	Cameroon	2004
Ndembi et al.	Western/Central Africa	Cameroon	2004
Koizumi et al.	Western/Central Africa	Cameroon	2004
Zhang et al.	Western Pacific	China	2004
Toni et al.	Western/Central Africa	Cote d'Ivoire	2004
Nafisa et al.	Eastern Africa	Kenya	2004
Viani et al.	Latin America	Mexico	2004
Lahuerta et al.	Eastern Africa	Mozambique	2004
Lyagoba et al.	Eastern Africa	Uganda	2004
Lyagoba et al.	Southern Africa	Zimbabwe	2004
Petroni et al.	Latin America	Argentina	2005
Tebit et al.	Western/Central Africa	Burkina Faso	2005
Marechal et al.	Western/Central Africa	CAR	2005
Zhong et al.	Western Pacific	China	2005
Liu et al.	Western Pacific	China	2005
Liao et al.	Western Pacific	China	2005
Lihana et al.	Eastern Africa	Kenya	2005
Derache et al.	Western/Central Africa	Mali	2005
Ahumada-Ruiz et al.	Latin America	Panama	2005
Diop-Ndiaye et al	Western/Central Africa	Senegal	2005
McIntyre et al.	Southern Africa	South Africa	2005
Orrell et al.	Southern Africa	South Africa	2005
Barth et al.	Southern Africa	South Africa	2005
Mosha et al.	Eastern Africa	Tanzania	2005
Nyombi et al.	Eastern Africa	Tanzania	2005
Apisarnthanarak et al.	South-East Asia	Thailand	2005
Lallemant et al.	South-East Asia	Thailand	2005
Ferreira et al.	Latin America	Brazil	2006
Oliveira et al.	Western/Central Africa	Cape Verde	2006
Liu et al.	Western Pacific	China	2006
Han et al.	Western Pacific	China	2006
Zhang et al.	Western Pacific	China	2006
Tu et al.	Western Pacific	China	2006
Murillo et al.	Latin America	Honduras	2006
Kandathil et al.	South-East Asia	India	2006
Kamoto et al.	Eastern Africa	Malawi	2006
Huang et al.	Southern Africa	South Africa	2006
van Zyl et al.	Southern Africa	South Africa	2006
Maphalala et al.	Southern Africa	Swaziland	2006
Apisarnthanarak et al.	South-East Asia	Thailand	2006
Sirivichayakul et al.	South-East Asia	Thailand	2006
Sirivichayakul et al.	South-East Asia	Thailand	2006
Auwanit et al.	South-East Asia	Thailand	2006
Rangel et al.	Latin America	Venezuela	2006
Thao Vu et al.	Western Pacific	Vietnam	2006
Pando et al.	Latin America	Argentina	2007
Bussmann et al.	Southern Africa	Botswana	2007
Sprinz et al.	Latin America	Brazil	2007
De sa Filho et al.	Latin America	Brazil	2007
Nouhin et al.	Western Pacific	Cambodia	2007
Aghokeng et al.	Western/Central Africa	Cameroon	2007
Burda et al.	Western/Central Africa	Cameroon	2007
Aghokeng et al.	Western/Central Africa	Cameroon	2007
Aghokeng et al.	Western/Central Africa	Cameroon	2007
Chunfu Yang et al.	Western Pacific	China	2007
Chin et al.	Western Pacific	China	2007
Djoko et al.	Western/Central Africa	DRC	2007
Chaturburj et al.	South-East Asia	India	2007
Lall et al.	South-East Asia	India	2007
Agwale et al.	Western/Central Africa	Nigeria	2007
Yaotse et al.	Western/Central Africa	Togo	2007
Lee et al.	Eastern Africa	Uganda	2007
Ishizaki et al.	Western Pacific	Vietnam	2007
Tshabalala et al	Southern Africa	Zimbabwe	2007
Zijenah et al.	Southern Africa	Zimbabwe	2007
Cardoso et al.	Latin America	Brazil	2008
Inocencio et al.	Latin America	Brazil	2008
Cardoso et al.	Latin America	Brazil	2008
Nzeyimana et al.	Eastern Africa	Burundi	2008
Diaz Granados et al.	Latin America	Columbia	2008
Rajesh et al.	South-East Asia	India	2008
Price et al.	Eastern Africa	Kenya	2008

Study	Region	Country	Mid-point year of recruitment
Haidara et al.	Western/Central Africa	Mali	2008
Avila-Rios et al.	Latin America	Mexico	2008
Price et al.	Eastern Africa	Rwanda	2008
Bessong et al.	Southern Africa	South Africa	2008
Price et al.	Eastern Africa	Uganda	2008
Castillo et al.	Latin America	Venezuela	2008
Phan et al.	Western Pacific	Vietnam	2008
Price et al.	Southern Africa	Zambia	2008
Castelbranco et al.	Southern Africa	Angola	2009
Arruda et al.	Latin America	Brazil	2009
Ferreira et al.	Latin America	Brazil	2009
Carvalho et al.	Latin America	Brazil	2009
Bacelar Acioli lins et al.	Latin America	Brazil	2009
Soares et al.	Latin America	Brazil	2009
Graf et al.	Latin America	Brazil	2009

Study	Region	Country	Mid-point year of recruitment
Diakite et al.	Western/Central Africa	Guinea-Canakry	2009
Lihana R et al.	Eastern Africa	Kenya	2009
Kamoto et al.	Eastern Africa	Malawi	2009
Mavhandu et al.	Southern Africa	South Africa	2009
Parboosing et al.	Southern Africa	South Africa	2009
Bontell et al.	Western Pacific	Vietnam	2009
Dean et al.	Western Pacific	Vietnam	2009
Ishizaki et al.	Western Pacific	Vietnam	2009
Tshabalala et al	Southern Africa	Zimbabwe	2009
Li et al.	Western Pacific	China	2010
Neogi et al.	South-East Asia	India	2010
Thorat et al.	South-East Asia	India	2010
Nazziwa et al.	Eastern Africa	Uganda	2010

Section 4. Methodological notes on the design and interpretation of WHO transmitted HIV drug resistance surveys

Surveys to monitor transmitted drug resistance sample individuals from populations likely to be antiretroviral drug–naive and to have been recently infected, in this case individuals younger than 25 years of age and, in the case of women, only those with no previous pregnancies or pregnant for the first time. Where available, evidence of recent infection or seroconversion by a valid laboratory test or evidence of a CD4 count exceeding 500 cells per mm^3 may also be used to determine eligibility. Consecutive HIV-positive specimens from eligible individuals diagnosed at sites offering services related to antenatal care, voluntary counselling and testing, sexually transmitted infections or preventing mother-to-child transmission may be used. In settings where the HIV epidemic is driven by a particular mode of transmission, HIV drug resistance transmission surveys can target a separate subpopulation (such as sex workers or people who inject drugs).

Briefly, the WHO HIV drug resistance survey method samples a small number ($n \leq 47$) of eligible individuals consecutively encountered at specific sites within an area during a limited time period. This method is not intended to estimate the point prevalence of transmitted HIV drug resistance but rather uses truncated sequential sampling to classify transmitted resistance for each drug class as low (prevalence lower than 5%), moderate (prevalence between 5% and 15%) or high (prevalence higher than 15%) *(2)*. Survey results are not intended to be representative of the countries from which they were reported and should not be generalized beyond the populations surveyed.

Because HIV serosurveys to estimate HIV prevalence in specific areas are already in place in most low- and middle-income countries *(3)*, WHO recommends using eligible remnant specimens from these surveys where possible. The survey only intends to collect epidemiological information that is routinely available from medical records. Dried blood spots are the most commonly used specimen type, and few surveys have used plasma or serum.

The results were considered if surveys were conducted according to WHO-recommended methods and if they satisfied the following four criteria: (1) the survey protocol and/or report was made available to WHO; (2) HIV drug resistance genotyping testing was performed in a WHO-designated laboratory; (3) the individual sequence data were quality assured by WHO; and (4) when requested, patient-level epidemiological information was made available to WHO for additional quality assurance of the data. Surveys conducted before 2007 that had HIV drug resistance genotyping conducted in a non-designated laboratory (at the time when the WHO laboratory network was not at its full capacity) were included in this report only if quality assurance of the raw sequence data and phylogenetic analysis conducted by WHO or a designated laboratory was considered satisfactory. Section 2 in this annex provides additional details on genotyping and quality assurance.

Individual sequences not passing the quality assurance assessment conducted by WHO were excluded from the analysis provided in this report and, consequently, some of the survey results presented herein may differ slightly from results from the same surveys published elsewhere.

WHO has updated and refined the methods and suggested public health and programmatic actions associated with surveys to assess transmitted HIV drug resistance. It is now recommended that different site types within a defined geographical region may be combined if one site type is anticipated to provide an insufficient sample size to make a prevalence classification during a maximum period of 12 months of specimen collection. In addition, alternative survey inclusion criteria are being considered to facilitate implementation in low-prevalence settings where standard criteria do not permit survey implementation.

Section 5. Measuring and classifying HIV drug resistance: the WHO HIV drug resistance surveillance mutations list and the Stanford HIV resistance database

Mutations occur randomly, and many are harmless. In fact, most mutations place HIV at a disadvantage by reducing the viral "fitness" and slowing its ability to infect cells. However, several mutations can actually give HIV a survival advantage when HIV medications are used, because these mutations can block drugs from working against the HIV enzymes they are designed to target.

HIV is also polymorphic. A position in an HIV genome is called polymorphic if it is different from what is observed in a standard laboratory reference strain of the virus. These nucleotide differences (polymorphisms) are commonly seen in the virus populations of infected individuals. Generally, polymorphisms have no impact on replication capacity and may even cause variants to replicate less well. However, polymorphisms in the presence of other major HIV drug resistance mutations may make the virus able to better replicate in the presence of drugs that would otherwise normally suppress their replication.

The WHO surveillance drug resistance mutations (SDRM) list published in 2007 and updated in 2009 consists of major drug resistance mutations selected for by antiretroviral use but excludes mutations considered to be polymorphic based on their prevalence in untreated subjects *(4)*. A threshold prevalence of 0.5% has been used to define a mutation as being polymorphic. As such, an assessment of HIV drug resistance based on the surveillance drug resistance mutation list identifies the presence or absence of major drug resistance mutations.

In 2012, published data from studies of untreated subjects were reanalysed using the Stanford HIV resistance database. Using these updated data, mutations at position 46 in protease (M46I or L) were found to have the highest prevalence of all the PI surveillance drug resistance mutations (0.21% and 0.26%, respectively). Based on a revised threshold of 0.2%, M46I and L have been removed from the list of mutations used to analyse the WHO survey data in this report. This effectively increases the specificity of the analysis although at the potential expense of reduced sensitivity. By reducing the prevalence threshold to differentiate a mutation from a polymorphism, the proportion of false-positives is likely to be reduced and the positive predictive value of the detection of PI resistance is likely to increase accordingly. For the purpose of analysis of baseline HIV drug resistance, the 2009 WHO surveillance mutations list, excluding mutations M46I and L, is used to identify mutations in baseline sequences.

The surveillance drug resistance mutation list was developed specifically to help identify HIV with evidence of prior drug exposure and to avoid considering naturally occurring polymorphisms as representing transmitted drug resistance. As such, the surveillance drug resistance mutation list was used for the purposes of the analysis of transmitted drug resistance (see Chapter 3) and resistance before antiretroviral therapy initiation (baseline of the survey of acquired drug resistance. see Chapter 4).

Nevertheless, some polymorphisms are known to contribute to reduced drug susceptibility. When drug resistance to antiretroviral drugs needs to be predicted, any mutations, including polymorphic mutations, known to contribute to susceptibility are considered and data are interpreted using a scoring system, or algorithm *(5)*, such as the one available on the Stanford HIV database web site (http://sierra2.stanford.edu/sierra/servlet/JSierra). The endpoints of WHO surveys of acquired HIV drug resistance are analysed within this framework, and a predicted resistance classification of low, moderate or high is considered as resistant (see Chapter 4).

In some cases, a drug resistance interpretation using this algorithm may result in a virus being classified as having low-level resistance in the absence of a mutation included in the surveillance drug resistance mutation list. Conversely, a virus may have one or more mutations as part of the surveillance drug resistance mutation list without having a sufficient number of mutations to result in a low-level drug resistance interpretation. This means that, when taking into account both major drug resistance

mutations and the effect that polymorphisms, if present, may have on the overall susceptibility of a drug to a particular HIV virus, it is not uncommon to see an absence of PI mutations based on the surveillance drug resistance mutation list but some level of predicted PI resistance (this is particularly true for nelfinavir and certain unboosted PI).

This pattern was observed among people initiating antiretroviral therapy in WHO acquired HIV drug resistance surveys. Only 28 people (0.6%) had any surveillance drug resistance mutation related to PI (Figure 4.4), but 611 people (12%) had at least low-level predicted resistance to a PI, nearly always (in 607 people) as a result of low-level predicted resistance to nelfinavir, based on the presence of multiple naturally occurring polymorphic mutations such as L10I or F, K20I and T74S (Figure 1 in Annex 2).[1] Similarly, while 187 people (3.7%) had at least one NNRTI surveillance drug resistance mutation (Figure 4.4), 290 people (5.7%) had at least low-level predicted resistance to an NNRTI (Figure 1 in Annex 2), nearly always as a result of low or intermediate-level predicted resistance to nevirapine, based on the presence of polymorphic mutations such as A98G, K103R and V179D, E138A, F227L and Y318F. One person had a rare Y181S mutation, which leads to an interpretation of low-level resistance to multiple NNRTI, but this mutation is not on the current surveillance drug resistance mutation list.

Section 6. Methods of the literature review on acquired drug resistance in low- and middle-income countries

PubMed, EMBASE and the Science Citation Index were searched for prospective or cross-sectional studies for the period between 1 January 1994 and 31 December 2011. The geographical focus was restricted to low- and middle-income countries from Asia (South-East Asia and Western Pacific Regions), sub-Saharan Africa (eastern, southern, western/central), Latin America and the Caribbean. Studies were included if they reported sequence data on at least 50 genotypes in people failing NNRTI-based first-line antiretroviral therapy at a median duration of therapy of 12 months.

Studies were excluded if they only reported resistance in the context of preventing mother-to-child transmission or used sequencing methods other than standard bulk sequencing, such as genome sequencing, allele-specific PCR and ultra-deep sequencing. Any published WHO HIV drug resistance surveys were also excluded.

Data on the clinical characteristics of population, history of antiretroviral therapy exposure and virological responses were abstracted. Definitions of virological failure, the proportions assessed for resistance and the resulting resistant genotypes were recorded. Study authors were contacted for further information if necessary. Mutations were defined according to internationally accepted lists.

Studies were either cohort studies, where people initiating NNRTI-based antiretroviral therapy were followed up, or cross-sectional, where participants were assessed for failure at 12 month or less. The variable common to each of these reports was the proportion of people carrying resistant virus among people failing antiretroviral therapy (number of people genotyped at failure with resistance divided by the number experiencing antiretroviral therapy failure with genotype available). Definitions of treatment failure included clinical, immunological and/or virological measures.

Study	Region	Country
Ndembi et al 2010	Eastern Africa	Uganda
Ramadhani et al 2007	Eastern Africa	Tanzania
Kouanfack et al 2009	West/Central Africa	Cameroon
Messou et al 2011	West/Central Africa	Ivory Coast
Dagnra et al 2011	West/Central Africa	Togo
Aghokeng et al 2011	West/Central Africa	Cameroon
Garrido et al 2008	Southern Africa	Angola
Zolfo et al 2011	Western Pacific	Cambodia
Ruan et al 2010	Western Pacific	China

Information on duration of therapy was derived at the study level as median duration, so the actual duration of therapy for individuals is distributed around the median. This implies that studies may include people who have been on therapy for more (or less) than 12 months. For instance, a study reporting a median duration of therapy of 12 months has up to 50% of observations above the median, therefore potentially including people who may have been receiving therapy for more than 12 months. In addition, resistance at treatment failure may have been related to the resistance already present at baseline, and participants recruited into these studies may not be representative of the general population with HIV on antiretroviral therapy.

1 Four people had drug resistance predicted to a ritonavir-boosted PI other than nelfinavir: atazanavir/r (I50L), fosamprenavir/r (multiple polymorphisms), indinavir/r (V82M) or tipranavir/r (multiple polymorphisms).

Section 7. Methodological notes on the design and interpretation of WHO acquired HIV drug resistance surveys

The research protocol stipulates that, at each antiretroviral therapy clinic being surveyed, a cohort of about 130 people initiating first-line antiretroviral therapy be enrolled. Drug resistance genotyping is performed before treatment initiation (baseline) for everyone, and everyone is then followed for 12 months. Consecutive individuals initiating first-line antiretroviral therapy at the selected site are eligible to participate in the survey, regardless of previous exposure to antiretroviral drugs for preventing mother-to-child transmission or other reasons. Baseline specimens are collected within one month before initiation of antiretroviral therapy. As patients who died or who were transferred to other facilities are not included in the analysis, an effective survey sample size of 96 patients with classifiable endpoints provides a 95% confidence interval of +/- 10% for the proportion with HIVDR prevention, regardless of the cumulative incidence of viral suppression. HIV is quantified (viral load) at 12 months for people maintained on first-line treatment or at the time of switch to second-line antiretroviral therapy for people experiencing therapy failure before 12 months. Among people with viral load exceeding 1000 copies/ml, genotyping is performed to characterize drug resistance mutations using population-base sequencing. Additional relevant demographic and epidemiological information is gathered, including previous exposure to antiretroviral drugs (for preventing mother-to-child transmission or previous antiretroviral therapy).

Although WHO prospective surveys of acquired HIV drug resistance have provided detailed site-specific information, their uptake had been limited because of their prospective nature, which required up to two years of follow-up to assess HIV drug resistance outcomes, and the relatively large sample size required. To address this challenge, a new cross-sectional method has been developed to assess acquired HIV drug resistance at representative antiretroviral therapy clinics among people for whom treatment is failing with detectable virus. This new method uses Lot Quality Assurance Sampling to classify the rates of viral load suppression 12–15 and 24–36 months after initiating antiretroviral therapy in adult populations and in paediatric populations receiving antiretroviral therapy for 12 or more months. Surveys are designed to be implemented routinely at representative sites in a country. Although WHO continues to support prospective surveys of acquired HIV drug resistance, the cross-sectional method is anticipated to be more easily implemented and provide more timely and more nationally representative results. This new cross-sectional method is currently being piloted in Namibia.

Section 8. The three outcomes of WHO acquired HIV drug resistance surveys: prevented, detected and possible HIV drug resistance

WHO surveys of acquired HIV drug resistance have three survey outcomes: HIV drug resistance prevention, HIV drug resistance and possible HIV drug resistance. Because death during the first year of treatment is unlikely to be attributable to HIV drug resistance and because HIV drug resistance outcomes for people transferring to other clinics cannot be used to assess the functioning of the sentinel sites, people with these survey endpoints are not included in the calculations of the estimated prevalence of HIV drug resistance prevention at 12 months.

1) HIV drug resistance prevention:

HIV drug resistance is considered to have been prevented if, 12 months after antiretroviral therapy initiation or at the time of the switch to second-line therapy, people have suppressed viral loads, defined as having less than 1000 copies/ml. A threshold of 1000 copies/ml was chosen because of sensitivity and reproducibility of standard commercial genotyping assays commonly available in low- and middle-income countries at the time the protocol was developed. The level of HIV drug resistance prevention in a cohort is assessed as follows:

Numerator: people with viral load less than 1000 copies/ml 12 months after antiretroviral therapy initiation or at the time of switch to second-line therapy

Denominator: people receiving first-line antiretroviral therapy at 12 months with classifiable viral load results + people switching to second-line antiretroviral therapy with classifiable viral load result + people lost to follow-up + people who stopped antiretroviral therapy during the survey.

2) HIV drug resistance:

HIV drug resistance is considered to have occurred if drug resistance is detected by genotyping in people with viral loads greater than 1000 copies/ml 12 months after antiretroviral therapy initiation or at the time of switch to second-line therapy. The prevalence of detected HIV drug resistance in a cohort is assessed as follows:

2a) HIV drug resistance (as a % of the people initiating therapy):

Numerator: people with a viral load greater than 1000 copies/ml 12 months after antiretroviral therapy initiation or at switch to second-line therapy with HIV drug resistance

Denominator: people receiving first-line antiretroviral therapy at 12 months with classifiable viral load results + people switching to second-line antiretroviral therapy with classifiable viral load result + people lost to follow-up + people who stopped antiretroviral therapy during the survey

2b) HIV drug resistance (as a % of people failing therapy with genotyping results available):

Numerator: people with viral load greater than 1000 copies/ml 12 months after antiretroviral therapy initiation or at switch to second-line antiretroviral therapy and HIV drug resistance

Denominator: people with viral load greater than 1000 copies/ml with genotyping available 12 months after antiretroviral therapy initiation or at the time of switching to second-line therapy

3) Possible HIV drug resistance:

HIV drug resistance is considered to be possible among people who (i) stopped antiretroviral therapy during the survey period, (ii) were lost to follow-up, (iii) had a viral load greater than 1000 copies/ml but failed to have a successful genotyping assay and (iv) had viral loads greater than 1000 copies/ml and no detected HIV drug resistance 12 months after antiretroviral therapy initiation or at the time of switching to second-line antiretroviral therapy:

Numerator: people with viral load greater than 1000 copies/ml and no detected HIV drug resistance at 12-month survey endpoint (on antiretroviral therapy at 12 months and at switch) + people who stopped antiretroviral therapy + people lost to follow-up + people with unclassifiable viral load at 12-month survey endpoint (on antiretroviral therapy at 12 months and at the time of switching to second-line therapy) + people with viral load greater greater than 1000 copies/ml but failed to have a successful genotyping assay.

Denominator: people on first-line antiretroviral therapy at 12 months with classifiable viral load results + people switching to second-line antiretroviral therapy with classifiable viral load result + people lost to follow-up + people who stopped antiretroviral therapy during the survey.

Section 9: Methods for statistical analyses

An exploratory analysis was performed and pooled proportions of the number of individuals with drug resistance mutations were determined. As the proportion of individuals with a drug resistance mutation was low, it was not possible to rely on the standard normal approximation to the binomial distribution to estimate pooled proportions. Instead, individual studies were transformed using a Freeman-Tukey-type arcsine square root transformation: $y=\arcsin[\sqrt{(r/(n+1)}] + \arcsin [\sqrt{(r+1)/(n+1)}]$, with a variance of $1/(n+1)$; where r is the number of individuals with a mutation, and n is the number of individuals genotyped. Using this procedure, confidence intervals for individual studies do not need to be symmetric on the natural scale and it is still possible to calculate confidence intervals when there are zero mutations. (Reference: Miller, J. J.The Inverse of the Freeman-Tukey Double Arcsine Transformation.The American Statistician, American Statistical Association, 1978, 32, p. 138).

Random effects meta-analyses were performed on the transformed proportions using DerSimonian-Laird weighting before back-transformation of the pooled proportions. Heterogeneity was assessed using the I^2 statistic from meta-analyses of the transformed proportions. Pooled proportions using this method were typically lower than what a simple pooling of data across studies would suggest. This is in line with (i) the low mutation rates observed in the available dataset and (ii) with the reduced variability, and therefore increased precision, of estimated mutation rates in studies where levels are close to 0 or 100% compared to when levels are close to 50% with an equal number of individuals genotyped.

In some surveys only partial sequence data were available (PR or RT regions only), so that when calculating the prevalence of "any drug resistance mutation", an average of the total number of genotypes with PR and RT sequences was used as the denominator.

Statistical analyses were conducted in Stata version 11.2 (StataCorp, Texas), including the use of the *metan* package for meta analysis and the *gllamm* package for mixed logistic regression models.

Analysis of change in levels of transmitted drug resistance by calendar year

To determine whether prevalence of transmitted resistance increased over time, data from all surveys were pooled according to region and sub-region, and year of implementation. To explore the significance of the observed variation over time, meta-regression was performed by using a mixed logistic regression model. Specifically these models included a fixed effect to account for differences between WHO regions, and random effects at the study level to account for between-study heterogeneity within each region. Models using random effects at the regional and country levels were also explored, without significant changes in the outcome.

Analysis of change in levels of HIV drug resistance by ART coverage

Meta-regressions were performed by using mixed logistic regression models including a fixed effect to account for differences between WHO regions, and random effects at the study level to account for between study heterogeneity within each region. To test for the importance of ART coverage or year, likelihood ratio tests were used to compare models with and without a linear term for ART coverage and baseline year. As the models are logistic regression models, coefficients from the model are log odds ratios, and so are linear on the log odds scale, but not on the natural scale. Due to the low prevalence of mutations, the odds ratio – which is the exponential of the coefficients from the logistic regression model – is approximately equal to the ratio of the mutation rates per 1 unit increase in the explanatory variable. Therefore, for a mutation rate of 1%, an odds ratio of 1.4% represents an increase to approximately 1.4%.

REFERENCES

1. Parkin N, Bremer J, Bertagnolio S. Genotyping external quality assurance in the World Health Organization HIV Drug Resistance Laboratory Network during 2007–2010. *Clinical Infectious Diseases*, 2012, 54(Suppl. 4):S266.
2. Myatt M, Bennett DE. A novel sequential sampling technique for the surveillance of transmitted HIV drug resistance by cross-sectional survey for use in low resource settings. *Antiviral Therapy,* 2008, 13(Suppl. 2):37–48.
3. UNAIDS/WHO Working Group on Global HIV/AIDS and STI Surveillance. *Guidelines for conducting HIV sentinel serosurveys among pregnant women and other groups*. Geneva, UNAIDS, 2003 (http://data.unaids.org/Publications/IRC-pub06/jc954-anc-serosurveys_guidelines_en.pdf?preview=true, accessed 28 June 2012).
4. Bennett DE et al. Drug resistance mutations for surveillance of transmitted HIV-1 drug-resistance: 2009 update. *PLoS One*, 2009, 4:e4724.
5. Liu TF, Shafer RW. Web resources for HIV type 1 genotypic-resistance test interpretation. *Clinical Infectious Diseases*, 2006, 42:1608–1618.

ANNEX 2. SUPPLEMENTAL TABLES AND FIGURES

Table 1 Prevalence of HIV drug resistance among antiretroviral therapy-naive individuals from the published literature, by year, region and class of antiretroviral drug (% with at least one drug resistance mutation (95% confidence interval)), 2003-2010

	WHO Region	2003	2004	2005	2006	2007	2008	2009	2010	p-value[a]
Any drug class	Africa	3.5 (1.6-5.8)	4.2 (1.1-8.8)	2.2 (0.8-4.0)	0.7 (0.0-2.3)	2.5 (0.8-4.9)	3.6 (2.2-5.4)	4.8 (3.1-6.7)	6.4 (1.3-17.5)	NS
	South-East Asia	1.6 (0.4-3.4)	—	1.0 (0.6-4.0)	1.3 (0.1-3.5)	3.3 (2.8-18.9)	2.9 (0.6-8.2)	—	1.0 (0.0-5.8)	NS
	Western Pacific	—	9.8 (0.9-25)	1.8 (0.2-4.5)	3.3 (1.0-6.6)	1.9 (0.6-3.7)	4.0 (1.6-8.2)	5.6 (3.2-8.7)	0.0 (0.0-16.1)	NS
	Latin America and the Caribbean	4.7 (2.3-7.6)	3.1 (1.7-4.9)	7.7 (2.1-18.5)	7.6 (4.8-10.9)	8.1 (4.0-13.4)	6.3 (5.3-7.5)	9.8 (7.5-12.4)	—	0.01
	Overall	3.6 (2.3-5.2)	4.5 (2.3-7.3)	1.9 (0.9-3.3)	2.5 (1.2-4.1)	3.1 (1.6-5.0)	4.9 (3.6-6.3)	6.6 (5.1-8.3)	2.1 (0.1-5.8)	0.03
NRTI	Africa	1.5 (0.4-3.1)	2.0 (0.4-4.6)	0.8 (0.0-2.2)	0.2 (0.0-0.3)	1.0 (0.0-2.7)	1.1 (0.3-2.2)	0.7 (0.1-1.7)	0.0 (0.0-7.5)	NS
	South-East Asia	0.3 (0.0-1.4)	—	0.9 (0.2-3.3)	1.0 (0.0-2.8)	2.5 (0.0-14.2)	1.9 (0.2-6.8)	—	0.0 (0.0-2.6)	NS
	Western Pacific	—	6.3 (0.1-18.8)	0.7 (0.0-2.0)	1.5 (0.1-3.9)	0.7 (0.0-2.1)	1.7 (0.4-5.0)	2.6 (0.7-10.1)	0.0 (0.0-16.1)	NS
	Latin America and the Caribbean	4.0 (1.9-6.6)	1.4 (0.3-2.9)	1.9 (0.0-10.3)	3.6 (1.2-7.1)	2.8 (0.9-5.6)	3.1 (1.8-4.6)	4.1 (2.0-6.8)	—	NS
	Overall	2.0 (0.9-3.4)	2.3 (1.0-4.0)	0.7 (0.1-1.5)	0.9 (0.1-2.2)	1.2 (0.4-2.4)	1.9 (1.1-2.9)	2.0 (0.8-3.5)	0.0 (0.0-1.4)	NS
NNRTI	Africa	1.0 (0.3-2.1)	0.6 (0.0-2.1)	1.1 (0.4-2.2)	0.2 (0.0-0.3)	0.7 (0.1-1.5)	2.1 (1.0-3.4)	3.3 (1.6-5.5)	6.4 (1.3-17.5)	0.01
	South-East Asia	0.1 (0.0-1.0)	—	0.7 (0.1-4.6)	1.1 (0.1-2.9)	0.0 (0.0-2.6)	1.0 (0.0-5.2)	—	0.0 (0.0-2.6)	NS
	Western Pacific	—	4.5 (0.7-22)	0.9 (0.2-3.4)	2.2 (0.8-4.1)	1.5 (0.4-3.1)	2.9 (0.9-6.6)	2.8 (0.5-6.5)	0.0 (0.0-16.1)	NS
	Latin America and the Caribbean	1.2 (0.1-4.2)	0.8 (0.1-1.9)	5.8 (1.2-15.9)	4.1 (2.1-6.7)	4.5 (2.1-7.7)	2.4 (1.1-4.0)	3.4 (2.0-5.2)	—	0.06
	Overall	0.9 (0.2-2.0)	1.0 (0.2-2.1)	1.1 (0.4-2.0)	1.2 (0.3-2.7)	1.2 (0.5-2.2)	1.8 (1.3-2.4)	3.3 (2.3-4.4)	0.9 (0.0-4.8)	<0.001
PI	Africa	0.1 (0.0-0.8)	0.8 (0.0-2.5)	0.0 (0.0-0.1)	0.2 (0.0-1.7)	0.1 (0.0-0.5)	0.4 (0.0-1.3)	0.1 (0.0-0.8)	0.0 (0.0-7.5)	NS
	South-East Asia	0.1 (0.0-1.2)	—	0.0 (0.0-0.3)	0.0 (0.0-0.4)	0.9 (0.0-5.2)	0.0 (0.0-3.5)	—	0.0 (0.0-2.6)	—
	Western Pacific	—	1.5 (0.0-4.1)	0.2 (0.0-0.8)	0.0 (0.0-0.4)	0.3 (0.0-0.2)	1.2 (0.1-4.1)	0.5 (0.0-2.4)	0.0 (0.0-16.1)	NS
	Latin America and the Caribbean	0.7 (0.0-2.1)	0.9 (0.0-2.8)	0.0 (0.0-6.8)	0.4 (0.2-1.7)	1.5 (0.3-3.2)	1.2 (0.7-1.8)	2.9 (1.6-4.6)	—	NS
	Overall	0.3 (0.0-1.0)	0.9 (0.2-2.0)	0.0 (0.0-0.1)	0.0 (0.0-0.3)	0.2 (0.0-0.6)	0.7 (0.3-1.4)	0.9 (0.2-1.9)	0.0 (0.0-1.4)	NS

a Statistical methods are described in Section 9, Annex 1.
NS: not statistically significant.
— Data not available or applicable.

Table 2 WHO surveys of transmitted HIV drug resistance with results classifiable for at least one drug class

WHO Region	Subregion	Country	Geographical area	Year of implementation	Population	NNRTI	NRTI	PI
Africa	Eastern	Ethiopia	Addis Ababa	2005	Pregnant women	<5%	<5%	<5%
Africa	Eastern	Kenya	Nairobi	2005	Pregnant women	<5%	<5%	<5%
Africa	Eastern	Kenya	Mombasa	2009	Voluntary counselling and testing attendees	5–15%	<5%	5–15%
Africa	Eastern	Malawi	Lilongwe	2006	Pregnant women	<5%	<5%	<5%
Africa	Eastern	Malawi	Blantyre	2009	Pregnant women	<5%	<5%	<5%
Africa	Eastern	Malawi	Lilongwe	2009	Pregnant women	5–15%	<5%	<5%
Africa	Eastern	Malawi	Lilongwe	2010	Pregnant women	5–15%	<5%	<5%
Africa	Eastern	Mozambique	Beira	2007	Pregnant women	<5%	5–15%	<5%
Africa	Eastern	Mozambique	Beira	2009	Pregnant women	5–15%	<5%	<5%
Africa	Eastern	Mozambique	Maputo	2009	Pregnant women	<5%	<5%	<5%
Africa	Eastern	United Republic of Tanzania	Dar es Salaam	2005	Pregnant women	<5%	<5%	<5%
Africa	Eastern	Uganda	Entebbe	2006	Pregnant women	<5%	<5%	<5%
Africa	Eastern	Uganda	Kampala	2008	Sex workers	NC	<5%	<5%
Africa	Eastern	Uganda	Kampala	2009	Voluntary counselling and testing attendees	<5%	5–15%	<5%
Africa	Southern	Angola	Luanda	2009	Pregnant women	<5%	<5%	<5%
Africa	Southern	Botswana	Francistown	2005	Pregnant women	<5%	<5%	<5%
Africa	Southern	Botswana	Gaborone	2005	Pregnant women	<5%	<5%	<5%
Africa	Southern	Botswana	Francistown	2007	Pregnant women	<5%	<5%	<5%
Africa	Southern	Lesotho	Maseru	2009	Pregnant women	NC	<5%	<5%
Africa	Southern	Namibia	Windhoek	2006	Pregnant women	<5%	<5%	<5%
Africa	Southern	South Africa	Gauteng	2004	Pregnant women	<5%	5–15%	NC
Africa	Southern	South Africa	Gauteng	2005	Pregnant women	<5%	<5%	NC
Africa	Southern	South Africa	KwaZulu-Natal	2005	Pregnant women	NC	<5%	NC
Africa	Southern	South Africa	Gauteng	2006	Pregnant women	<5%	<5%	<5%
Africa	Southern	South Africa	Gauteng	2007	Pregnant women	<5%	<5%	<5%
Africa	Southern	South Africa	KwaZulu-Natal	2007	Pregnant women	<5%	<5%	<5%
Africa	Southern	South Africa	Gauteng	2008	Pregnant women	<5%	<5%	<5%
Africa	Southern	South Africa	KwaZulu-Natal[a]	2008	Pregnant women	5–15%	5–15%	<5%
Africa	Southern	South Africa	Gauteng	2009	Pregnant women	<5%	<5%	<5%
Africa	Southern	South Africa	KwaZulu-Natal	2009	Pregnant women	5–15%	<5%	<5%
Africa	Southern	South Africa	Gauteng	2010	Pregnant women	<5%	<5%	<5%
Africa	Southern	South Africa	KwaZulu-Natal	2010	Pregnant women	5–15%	5–15%	<5%

Table 2 WHO surveys of transmitted HIV drug resistance with results classifiable for at least one drug class (cont.)

WHO Region	Subregion	Country	Geographical area	Year of implementation	Population	NNRTI	NRTI	PI
Africa	Southern	Swaziland	Manzini-Mbabane	2006	Pregnant women	<5%	<5%	<5%
Africa	Southern	Swaziland	Manzini-Mbabane	2008	Pregnant women	<5%	<5%	<5%
Africa	Southern	Swaziland	Shiselweni	2010	Pregnant women	<5%	<5%	<5%
Africa	Western/central	Burkina Faso	Bobo Dioulasso	2005	Pregnant women	<5%	<5%	<5%
Africa	Western /central	Burkina Faso	Ouagadougou	2009	Pregnant women	5–15%	5–15%	<5%
Africa	Western/central	Cameroon	Douala	2006	Pregnant women	<5%	5–15%	<5%
Africa	Western/central	Cameroon	Yaoundé	2006	Pregnant women	5–15%	<5%	<5%
Africa	Western/central	Chad	N'Djamena	2006	Pregnant women	<5%	<5%	<5%
Africa	Western/central	Cote d'Ivoire	Abidjan	2008	Pregnant women	<5%	<5%	<5%
Africa	Western/central	Ghana	Manya Krobo	2008	Pregnant women	<5%	<5%	<5%
Africa	Western/central	Senegal	Dakar	2007	Voluntary counselling and testing attendees	<5%	<5%	<5%
Americas		Mexico	Mexico City	2004	Voluntary counselling and testing attendees	<5%	5–15%	<5%
European		Ukraine	Donetsk	2009	Voluntary counselling and testing attendees	<5%	<5%	<5%
European		Ukraine	Kherson	2009	Voluntary counselling and testing attendees	NC	<5%	NC
European		Ukraine	Kyiv[a]	2009	Voluntary counselling and testing attendees	NC	5–15%	NC
European		Ukraine	Odessa	2009	Voluntary counselling and testing attendees	<5%	<5%	<5%
South-East Asia		India	Kakinada	2007	Pregnant women	<5%	<5%	<5%
South-East Asia		India	Mumbai	2007	Voluntary counselling and testing attendees	<5%	<5%	NC
South-East Asia		Indonesia	Jakarta	2006	People who inject drugs	<5%	<5%	<5%
South-East Asia		Thailand	Bangkok	2005	Voluntary counselling and testing attendees	<5%	NC	<5%
South-East Asia		Thailand	Bangkok	2005	Blood donors	<5%	<5%	<5%
South-East Asia		Thailand	Chiang Mai	2007	Pregnant women	<5%	<5%	<5%
Western Pacific		Cambodia	Phnom Penh[a]	2008	Voluntary counselling and testing attendees	5–15%	NC	<5%
Western Pacific		China	Hunan	2007	Voluntary counselling and testing attendees	<5%	<5%	<5%
Western Pacific		China	Beijing	2008	Voluntary counselling and testing attendees	<5%	<5%	<5%
Western Pacific		China	Shenzhen (Guangdong)	2008	Voluntary counselling and testing attendees	<5%	<5%	<5%
Western Pacific		China	Liangshan (Sichuan)	2008	Voluntary counselling and testing attendees	<5%	<5%	<5%
Western Pacific		China	Urumqi City (Xinjiang)	2008	Voluntary counselling and testing attendees	<5%	NC	5–15%
Western Pacific		China	Yili City (Xinjiang)	2008	Voluntary counselling and testing attendees	<5%	<5%	<5%
Western Pacific		China	Kunming (Yunnan)	2008	Voluntary counselling and testing attendees	<5%	<5%	<5%
Western Pacific		China	Beijing	2009	Voluntary counselling and testing attendees	<5%	<5%	<5%
Western Pacific		China	Guizhou	2009	Voluntary counselling and testing attendees	<5%	<5%	<5%
Western Pacific		China	Hunan	2009	Voluntary counselling and testing attendees	5–15%	<5%	<5%

Table 2 WHO surveys of transmitted HIV drug resistance with results classifiable for at least one drug class (cont.)

WHO Region	Subregion	Country	Geographical area	Year of implementation	Population	NNRTI	NRTI	PI
Western Pacific		China	Jiangsu	2009	Voluntary counselling and testing attendees	<5%	<5%	<5%
Western Pacific		China	Shenzhen (Guangdong)	2009	Voluntary counselling and testing attendees	<5%	<5%	<5%
Western Pacific		China	Liangshan (Sichuan)	2009	Voluntary counselling and testing attendees	<5%	<5%	<5%
Western Pacific		China	Dehong (Yunnan)	2009	Voluntary counselling and testing attendees	<5%	<5%	<5%
Western Pacific		China	Zhejiang	2009	Voluntary counselling and testing attendees	<5%	5-15%	<5%
Western Pacific		Viet Nam	Hanoi	2006	Voluntary counselling and testing attendees	<5%	<5%	<5%
Western Pacific		Viet Nam	Ho Chi Minh City	2007	Voluntary counselling and testing attendees	5-15%	<5%	<5%
Overall totals					Not classifiable	5	3	6
					<5%	55	59	64
					5-15%	12	10	2
					>15%	0	0	0
Total						72	72	72

a Moderate classifications designated although specimen number does not permit distinction between moderate and high.
NC: not classifiable.

Table 3 Countries with at least two WHO transmitted drug resistance surveys repeated over time, by year of survey, 2004–2010[a]

		Year of Implementation						
Region	Country	2004	2005	2006	2007	2008	2009	2010
Africa	Botswana		Francistown; Gaborone		Francistown			
Africa	Burkina Faso		Bobo Dioulasso				Ouagadougou (NNRTI+NRTI)	
Africa	Kenya		Nairobi				Mombasa (NNRTI+PI)	
Africa	Malawi			Lilongwe			Lilongwe (NNRTI); Blantyre	Lilongwe (NNRTI)
Africa	Mozambique				Beira (NRTI)		Beira (NNRTI); Maputo	
Africa	South Africa	Gauteng (NRTI)	Gauteng; KwaZulu-Natal	Gauteng	Gauteng; KwaZulu-Natal	Gauteng; KwaZulu-Natal (NNRTI + NRTI)	Gauteng; KwaZulu-Natal (NNRTI)	Gauteng; KwaZulu-Natal (NNRTI+NRTI)
Africa	Swaziland			Manzini-Mbabane		Manzini-Mbabane		Shiselweni
Africa	Uganda[b]			Entebbe		Kampala	Kampala (NRTI)	
South East Asia	Thailand		Bangkok (2)		Chiang Mai			
Western Pacific	China				Hunan	Beijing; Kunming; Liangshan; Shenzhen; Urumqi city (PI); Yili city	Beijing; Dehong; Guizhou; Hunan (NNRTI); Jiangsu; Liangshan; Shenzhen; Zhejiang (NRTI)	
Western Pacific	Viet Nam			Hanoi	Ho Chi Minh City (NNRTI)			

a Areas with moderate classification of transmitted drug resistance are in red.
b Entebbe and Kampala in Uganda are considered as the same geographic area.

Table 4 Transmitted drug resistance surveys with moderate classification (between 5% and 15%) drug resistance

Drug class	number of surveys with moderate classification	Africa				Latin America and the Caribbean	Europe	South-East Asia	Western Pacific
		Eastern	Southern	Western/Central	Africa total				
Any	20	6 (30%)[a]	4 (20%)	3 (15%)	13 (65%)	1 (5%)	1 (5%)	0 (0%)	5 (25%)
NNRTI	12	4 (33.3%)	3 (25%)	2 (16.7%)	9 (75%)	0 (0%)	0 (0%)	0 (0%)	3 (25%)
NRTI	10	2 (20%)	3 (30%)	2 (20%)	7 (70%)	1 (10%)	1 (10%)	0 (0%)	1 (10%)
PI	2	1 (50%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)
NNRTI and NRTI	3	0 (0%)	2 (66.7%)	1 (33.3%)	3 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total number of surveys	72	14	21	8	43	1	4	6	18

a Percentages are out of the number for each drug class category.

Table 5 Estimated prevalence of mutations in WHO acquired drug resistance surveys at baseline by region and by drug class % (95% confidence intervals), 2007-2010

		Year of Implementation				
	WHO Region	2007	2008	2009	2010	p-value[a]
Any drug class	Africa	4.6 (3.6-5.8)	3.7 (2.8-4.8)	4.6 (2.2-7.8)	6.8 (4.8-9.0)	0.04
	South-East Asia	7.9 (4.0-13.7)	5.4 (2.9-8.6)	—	—	0.34
	Overall	4.8 (3.8-6.0)	3.9 (3.0-4.9)	4.6 (2.2-7.8)	6.8 (4.8-9.0)	0.06
NRTI	Africa	1.1 (0.6-1.7)	1.0 (0.5-1.6)	1.1 (0.3-2.2)	1.0 (0.3-2.0)	0.75
	South-East Asia	3.6 (1.2-8.2)	4.3 (2.0-7.2)	—	—	0.74
	Overall	1.2 (0.7-2.0)	1.3 (0.8-2.0)	1.1 (0.3-2.2)	1.0 (0.3-2.0)	0.70
NNRTI	Africa	3.4 (2.4-4.5)	2.3 (1.4-3.3)	3.3 (1.8-5.0)	5.4 (3.7-7.4)	0.03
	South-East Asia	7.9 (4.0-13.7)	3.0 (1.2-5.6)	—	—	—
	Overall	3.7 (2.5-4.9)	2.4 (1.6-3.3)	3.3 (1.8-5.0)	5.4 (3.7-7.4)	0.06
PI	Africa	0.3 (0.1-0.8)	0.5 (0.1-0.9)	0.5 (0.1-1.7)	0.0 (0.0-0.4)	0.82
	South-East Asia	0.0 (0.0-2.6)	0.0 (0.0-0.7)	—	—	—
	Overall	0.3 (0.0-0.7)	0.4 (0.1-0.8)	0.5 (0.1-1.7)	0.0 (0.0-0.4)	0.97

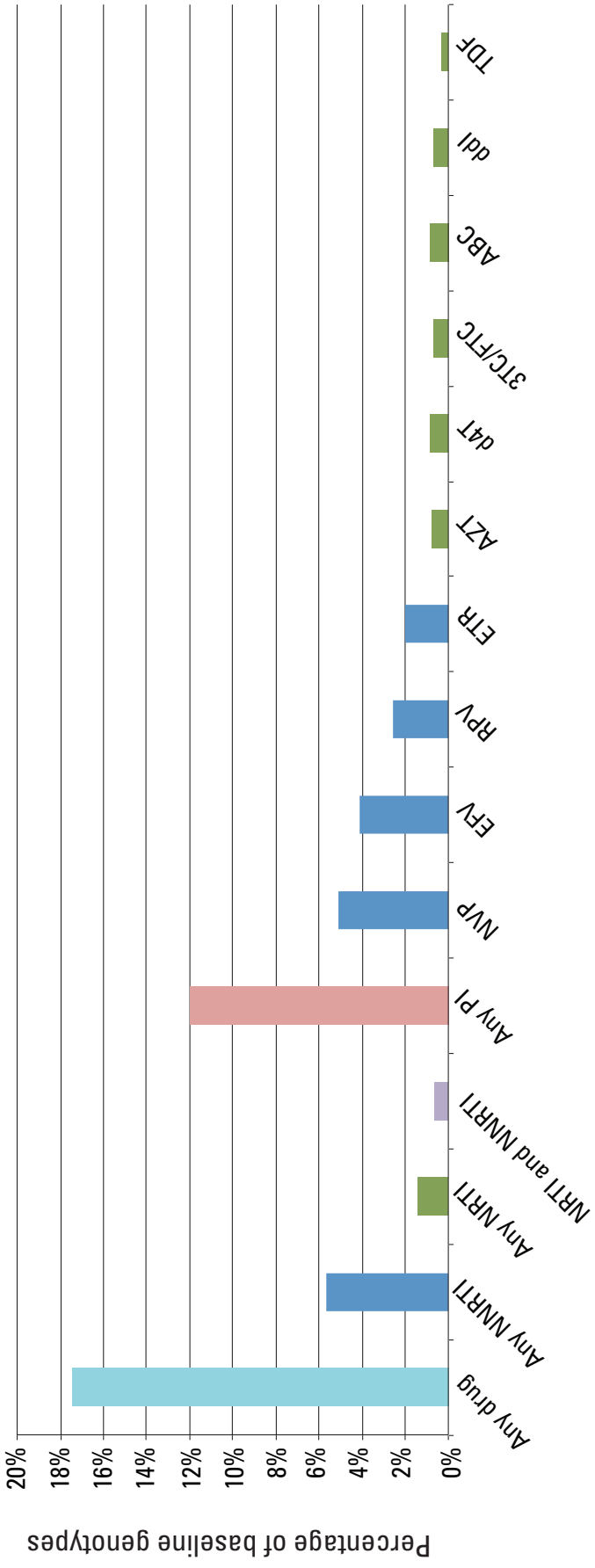
a Statistical methods are described in Section 9, Annex 1.
— Data are not available or applicable.

Table 6 Prior exposure to antiretroviral drugs and detection of resistance mutations at baseline, by individual WHO HIV drug resistance survey

Survey	Number of people with genotypes administered a questionnaire on previous exposure to ARVs (A)	Number of people reporting previous exposure to ARVs (including for PMTCT) (B)	Number of people reporting previous exposure to ARVs with RT SDRM at baseline (C)	Number of people reporting previous exposure to ARVs without RT SDRM at baseline (D)	Number of people reporting no previous exposure to ARVs with RT SDRM at baseline (E)	Number of people reporting no previous exposure to ARVs without RT SDRM at baseline (F)	% reporting previous exposure to ARVs with RT SDRM at baseline (C/(C+D))	% reporting no previous exposure to ARVs with RT SDRM at baseline (E/(E+F))
Kenya-1 2007	210	9	2	7	6	195	22.2%	3.0%
Kenya-2 2008	206	6	0	6	7	193	0.0%	3.5%
South Africa-1 2007	211	4	4	0	8	199	100.0%	3.9%
South Africa-2 2007	196	19	6	13	2	175	31.6%	1.1%
South Africa-3 2007	183	10	3	7	6	167	30.0%	3.5%
Zambia-1 2007	219	4	1	3	7	208	25.0%	3.3%
Zambia-2 2007	208	10	4	6	7	191	40.0%	3.5%
Zambia-3 2007	104	4	0	4	6	94	0.0%	6.0%
Zimbabwe-1 2008	206	14	3	11	4	188	21.4%	2.1%
Zimbabwe-2 2009	126	17	0	17	4	105	0.0%	3.7%
Zimbabwe-3 2009	124	7	1	6	4	113	14.3%	3.4%
Zimbabwe-4 2009	133	27	2	25	8	98	7.4%	7.5%
Zimbabwe-5 2010	24	3	1	2	1	20	33.3%	4.8%
Zimbabwe-6 2010	48	8	2	6	5	35	25.0%	12.5%
Zimbabwe-7 2010	149	79	3	76	2	68	3.8%	2.9%
Zimbabwe-8 2010	112	10	0	10	7	95	0.0%	6.9%
Zimbabwe-9 2010	110	10	0	10	9	91	0.0%	9.0%
Zimbabwe-10 2010	10	1	0	1	2	7	0.0%	22.2%
Zimbabwe-11 2010	132	19	1	18	6	107	5.3%	5.3%
Zimbabwe-12 2010	129	6	2	4	5	118	33.3%	4.1%
Cameroon-1 2009	141	2	0	2	3	136	0.0%	2.2%
Nigeria-3 2008	195	2	1	1	4	189	50.0%	2.1%
India-1 2007	140	11	5	6	6	123	45.5%	4.7%
India-2 2008	148	4	3	1	5	139	75.0%	3.5%
	3464	286	44	242	124	3054	15.4%	3.9%

RT: reverse transcriptase. SDRM: surveillance drug resistance mutation.

Figure 1 Predicted HIV drug resistance in people initiating antiretroviral therapy (WHO HIV drug resistance survey baseline specimens)[a]



a Detailed methodological notes are available in Section 5, Annex 1.

Table 7 WHO Acquired HIV drug resistance survey endpoints

WHO Region	Subregion	Survey	Number of people enrolled	People receiving first-line ART at 12 months n	Lost to follow-up n (%)	Stopped ART n (%)	Transferred out n (%)	Deaths n (%)	Switch to second line n (%)	Unclassifiable n (%)
Africa	Eastern	Burundi-1 2007	125	114	1 (0.8%)	—	1 (0.8%)	9 (7.2%)	—	—
Africa	Eastern	Burundi-2 2007	136	126	3 (2.2%)	—	3 (2.2%)	3 (2.2%)	—	1 (0.7%)
Africa	Eastern	Kenya-1 2007	221	181	17 (7.7%)	—	8 (3.6%)	15 (6.8%)	—	—
Africa	Eastern	Kenya-2 2008	223	205	10 (4.5%)	1 (0.4%)	5 (2.2%)	2 (0.9%)	—	—
Africa	Eastern	Malawi-1 2006	148	74	24 (16.2%)	5 (3.4%)	28 (18.9%)	17 (11.5%)	—	—
Africa	Eastern	Malawi-2 2006	143	89	28 (19.6%)	—	14 (9.8%)	12 (8.4%)	—	—
Africa	Eastern	Malawi-3 2006	145	95	20 (13.8%)	—	13 (9%)	17 (11.7%)	—	—
Africa	Eastern	Malawi-4 2006	160	73	7 (4.4%)	—	62 (38.8%)	18 (11.3%)	—	—
Africa	Eastern	Malawi-1 2008	153	112	9 (5.9%)	—	13 (8.5%)	16 (10.5%)	—	3 (2%)
Africa	Eastern	Malawi-2 2008	150	108	20 (13.3%)	—	8 (5.3%)	12 (8%)	—	2 (1.3%)
Africa	Eastern	Malawi-3 2008	150	99)	26 (17.3%)	—	14 (9.3%)	10 (6.7%)	—	1 (0.7%)
Africa	Eastern	Malawi-4 2008	150	117	12 (8%)	—	7 (4.7%)	11 (7.3%)	—	3 (2%)
Africa	Eastern	Mozambique-1 2007	119	101	12 (10.1%)	—	—	6 (5%)	—	—
		Eastern Africa	2023	1494	189 (9.3%)	6 (0.3%)	176 (8.7%)	148 (7.3%)	0 (0%)	10 (0.5%)
Africa	Southern	South Africa-1 2007	224	176	13 (5.8%)	—	11 (4.9%)	23 (10.3%)	1 (0.4%)	—
Africa	Southern	South Africa-2 2007	205	169	12 (5.9%)	1 (0.5%)	8 (3.9%)	14 (6.8%)	1 (0.5%)	—
Africa	Southern	South Africa-3 2007	208	166	18 (8.7%)	—	12 (5.8%)	11 (5.3%)	1 (0.5%)	—
Africa	Southern	Swaziland-1 2008	133	69	27 (20.3%)	—	20 (15%)	15 (11.3%)	—	2 (1.5%)
Africa	Southern	Swaziland-2 2008	127	69	48 (37.8%)	—	8 (6.3%)	2 (1.6%)	—	—
Africa	Southern	Zambia-1 2007	239	167	30 (12.6%)	—	13 (5.4%)	27 (11.3%)	2 (0.8%)	—
Africa	Southern	Zambia-2 2007	228	197	6 (2.6%)	4 (1.8%)	4 (1.8%)	17 (7.5%)	—	—
Africa	Southern	Zambia-3 2007	116	85	10 (8.6%)	—	1 (0.9%)	20 (17.2%)	—	—
Africa	Southern	Zimbabwe-1 2008	230	216	4 (1.7%)	—	3 (1.3%)	7 (3%)	—	—
		Southern Africa	1710	1314	168 (9.8%)	5 (0.3%)	80 (4.7%)	136 (8%)	5 (0.3%)	2 (0.1%)
Africa	Western/Central	Cameroon-1 2009	141	76	47 (33.3%)	-	5 (3.5%)	13 (9.2%)	-	-
Africa	Western/Central	Nigeria-1 2008	140	90	43 (30.7%)	-	2 (1.4%)	5 (3.6%)	-	-
Africa	Western/Central	Nigeria-2 2008	143	84	54 (37.8%)	-	1 (0.7%)	4 (2.8%)	-	-
Africa	Western/Central	Nigeria-3 2008	208	153	40 (19.2%)	-	4 (1.9%)	9 (4.3%)	2 (1%)	-
		Western/Central Africa	1710	1314	168 (9.8%)	5 (0.3%)	80 (4.7%)	136 (8%)	5 (0.3%)	2 (0.1%)
		Africa	4365	3211	541 (12.4%)	11 (0.3%)	268 (6.1%)	315 (7.2%)	7 (0.2%)	12 (0.3%)
South-East Asia		India-1 2007	141	88	28 (19.9%)	—	11 (7.8%)	13 (9.2%)	—	1 (0.7%)
South-East Asia		India-2 2008	148	104	19 (12.8%)	1 (0.7%)	10 (6.8%)	14 (9.5%)	—	—
South-East Asia		Indonesia-1 2008	110	72	11 (10%)	1 (0.9%)	5 (4.5%)	20 (18.2%)	—	1 (0.9%)
		South-East Asia	399	264	58 (14.5%)	2 (0.5%)	26 (6.5%)	47 (11.8%)	0 (0%)	2 (0.5%)
Overall			4764	3475	599 (12.6%)	13 (0.3%)	294 (6.2%)	362 (7.6%)	7 (0.1%)	14 (0.3%)

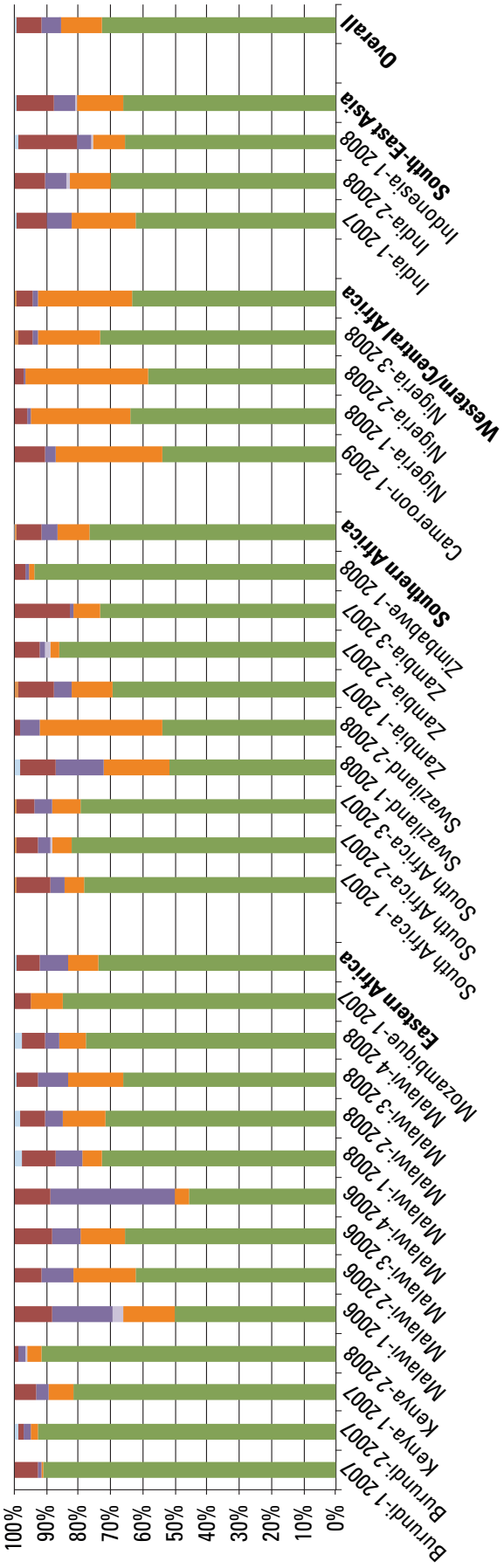


Figure 2 WHO acquired drug resistance survey endpoints, by clinic surveyed

Table 8 WHO HIV drug resistance survey outcomes (HIV drug resistance; HIV drug resistance prevention; HIV drug resistance possible), by individual antiretroviral therapy clinic

WHO Region	Subregion	Survey	Urban/rural	Site type	People with RT SDRM at ART initiation (%)	HIV drug resistance prevention (% of people initiating ART[b])	Any HIV drug resistance at endpoint[a] (% of people initiating ART[b])	Any HIV drug resistance at endpoint[a] (% of people failing with genotypes)	HIV drug resistance possible (% of people initiating ART[b])
Africa	Eastern	Burundi-1 2007	Urban	Private	1.8%	84.4%	2.8%	25.0%	12.8%
Africa	Eastern	Burundi-2 2007	Urban	Public	0.8%	80.6%	4.6%	27.8%	14.8%
Africa	Eastern	Kenya-1 2007	Urban	Public with external support	3.3%	82.6%	2.6%	41.7%	14.7%
Africa	Eastern	Kenya-2 2008	Urban	Private	2.9%	86.1%	4.1%	100.0%	9.8%
Africa	Eastern	Malawi-1 2006	Urban	Public with external support	—	60.0%	2.5%	66.7%	37.5%
Africa	Eastern	Malawi-2 2006	Urban	Public	—	67.6%	4.8%	83.3%	27.6%
Africa	Eastern	Malawi-3 2006	Urban	Public	—	79.1%	2.7%	100.0%	18.2%
Africa	Eastern	Malawi-4 2006	Urban	Public with external support	—	83.1%	3.4%	66.7%	13.6%
Africa	Eastern	Malawi-1 2008	Urban	Public with external support	6.7%	85.0%	5.8%	77.8%	9.2%
Africa	Eastern	Malawi-2 2008	Urban	Public	3.5%	74.8%	4.9%	83.3%	20.4%
Africa	Eastern	Malawi-3 2008	Urban	Public	2.9%	73.3%	2.5%	60.0%	24.2%
Africa	Eastern	Malawi-4 2008	Urban	Public with external support	4.0%	83.2%	6.7%	100.0%	10.1%
Africa	Eastern	Mozambique-1 2007	Urban	Public	7.0%	79.8%	8.3%	100.0%	11.9%
				Eastern Africa	3.6%	79.4%	4.3%	63.7%	16.4%
Africa	Southern	South Africa-1 2007	Rural	Private	5.7%	85.3%	3.8%	58.3%	10.9%
Africa	Southern	South Africa-2 2007	Urban	Private	4.1%	82.9%	6.1%	71.4%	11.0%
Africa	Southern	South Africa-3 2007	Urban	Public with external support	4.9%	86.0%	0.6%	50.0%	13.5%
Africa	Southern	Swaziland-1 2008	Rural	Private	3.2%	61.8%	6.7%	85.7%	31.5%
Africa	Southern	Swaziland-2 2008	Urban	Public	2.4%	50.0%	3.8%	80.0%	46.2%
Africa	Southern	Zambia-1 2007	Urban	Private	3.7%	78.1%	2.7%	62.5%	19.3%
Africa	Southern	Zambia-2 2007	Urban	Private	5.3%	85.2%	7.4%	83.3%	7.4%
Africa	Southern	Zambia-3 2007	Urban	Private	5.8%	77.9%	7.0%	66.7%	15.1%
Africa	Southern	Zimbabwe-1 2008	Urban	Private	3.4%	90.4%	5.5%	80.0%	4.1%
Africa	Southern	Zimbabwe-2 2009	Rural	Private	3.0%	—	—	—	—
Africa	Southern	Zimbabwe-3 2009	Urban	Public	4.0%	—	—	—	—
Africa	Southern	Zimbabwe-4 2009	Rural	Public	7.5%	—	—	—	—

Table 8 WHO HIV drug resistance survey outcomes (HIV drug resistance; HIV drug resistance prevention; HIV drug resistance possible), by individual antiretroviral therapy clinic (cont.)

WHO Region	Subregion	Survey	Urban/rural	Site type	People with RT SDRM at ART initiation (%)	HIV drug resistance prevention (% of people initiating ART[b])	Any HIV drug resistance at endpoint[a] (% of people initiating ART[b])	Any HIV drug resistance at endpoint[a] (% of people failing with genotypes)	HIV drug resistance possible (% of people initiating AR[b])
Africa	Southern	Zimbabwe-5 2010	Urban	Public	7.1%	—	—	—	—
Africa	Southern	Zimbabwe-6 2010	Peri-Urban	Private	12.5%	—	—	—	—
Africa	Southern	Zimbabwe-7 2010	Rural	Private	4.6%	—	—	—	—
Africa	Southern	Zimbabwe-8 2010	Urban	Public	6.1%	—	—	—	—
Africa	Southern	Zimbabwe-9 2010	Rural	Private	8.8%	—	—	—	—
Africa	Southern	Zimbabwe-10 2010	Rural	Public	20.0%	—	—	—	—
Africa	Southern	Zimbabwe-11 2010	Rural	Public	6.0%	—	—	—	—
Africa	Southern	Zimbabwe-12 2010	Urban	Public	5.0%	—	—	—	—
				Southern Africa	5.1%	80.3%	4.7%	73.3%	15.0%
Africa	Western/Central	Cameroon-1 2009	Urban	Public	2.2%	56.1%	3.3%	66.7%	40.7%
Africa	Western/Central	Nigeria-1 2008	Urban	Public	0.7%	59.4%	4.5%	54.5%	36.1%
Africa	Western/Central	Nigeria-2 2008	Urban	Public	4.5%	51.1%	9.5%	100.0%	39.4%
Africa	Western/Central	Nigeria-3 2008	Urban	Public with external support	2.6%	69.1%	6.3%	70.6%	24.6%
				Western/Central Africa	2.5%	59.9%	6.0%	74.5%	34.1%
Africa					4.3%	76.5%	4.7%	69.5%	18.8%
South-East Asia	—	India-1 2007	Urban	Public	7.9%	67.0%	7.8%	90.0%	25.2%
South-East Asia	—	India-2 2008	Urban	Public	5.4%	73.4%	9.7%	92.3%	16.9%
South-East Asia	—	Indonesia-1 2008	Urban	Public	5.5%	75.0%	9.2%	100.0%	15.8%
South-East Asia					6.3%	71.4%	8.9%	93.3%	19.7%
Overall					4.5%	76.1%	5.1%	72.1%	18.8%

RT: reverse transcriptase. SDRM: surveillance drug resistance mutation. NA: not available. a HIV drug resistance defined as a drug resistance prediction of low, intermediate or high level using the Stanford HIV database algorithm. Alternatively, if calculated based on the number of surveillance drug resistance mutations at endpoint, subregional, regional and overall proportions remain identical. b Excludes people who died or who were transferred to another antiretroviral therapy facility.

— Data are not available or applicable.

a HIV drug resistance defined as a drug resistance prediction of low, intermediate or high level using the Stanford HIV database algorithm. Alternatively, if calculated based on the number of surveillance drug resistance mutations at endpoint, subregional, regional and overall proportions remain identical.

b Excludes people who died or who were transferred to another antiretroviral therapy facility.

Table 9 WHO acquired drug resistance survey: "HIV drug resistance" outcome, by individual antiretroviral therapy clinic

WHO Region	Subregion	Survey	People enrolled (A)	People receiving first-line ART at 12 months with viral load results classifiable (B)	People switching with viral load classifiable (C)	Lost to follow-up (D)	Stopped ART (E)	Denominator for calculating outcomes (F: B+C+D+E)	People with viral load >1000 copies/ml and genotyped at 12 months or switch (G)	Numerator outcome 2: people with any HIVDR at 12 months or switch (H)	People with any HIVDR at 12 months or switch among those genotyped (H/G)	Outcome 2: HIVDR at 12 months or switch (H/F)
Africa	Eastern	Burundi-1 2007	125	108	0	1	0	109	12	3	25.0%	2.8%
Africa	Eastern	Burundi-2 2007	136	105	0	3	0	108	18	5	27.8%	4.6%
Africa	Eastern	Kenya-1 2007	221	173	0	17	0	190	12	5	41.7%	2.6%
Africa	Eastern	Kenya-2 2008	223	183	0	10	1	194	8	8	100.0%	4.1%
Africa	Eastern	Malawi-1 2006	148	51	0	24	5	80	3	2	66.7%	2.5%
Africa	Eastern	Malawi-2 2006	143	77	0	28	0	105	6	5	83.3%	4.8%
Africa	Eastern	Malawi-3 2006	145	90	0	20	0	110	3	3	100.0%	2.7%
Africa	Eastern	Malawi-4 2006	160	52	0	7	0	59	3	2	66.7%	3.4%
Africa	Eastern	Malawi-1 2008	153	111	0	9	0	120	9	7	77.8%	5.8%
Africa	Eastern	Malawi-2 2008	150	83	0	20	0	103	6	5	83.3%	4.9%
Africa	Eastern	Malawi-3 2008	150	94	0	26	0	120	5	3	60.0%	2.5%
Africa	Eastern	Malawi-4 2008	150	107	0	12	0	119	8	8	100.0%	6.7%
Africa	Eastern	Mozambique-1 2007	119	97	0	12	0	109	9	9	100.0%	8.3%
		Eastern Africa	2023	1331	0	189	6	1526	102	65	63.7%	4.3%
Africa	Southern	South Africa-1 2007	224	170	1	13	0	184	12	7	58.3%	3.8%
Africa	Southern	South Africa-2 2007	205	150	1	12	1	164	14	10	71.4%	6.1%
Africa	Southern	South Africa-3 2007	208	153	0	18	0	171	2	1	50.0%	0.6%
Africa	Southern	Swaziland-1 2008	133	62	0	27	0	89	7	6	85.7%	6.7%
Africa	Southern	Swaziland-2 2008	127	58	0	48	0	106	5	4	80.0%	3.8%
Africa	Southern	Zambia-1 2007	239	157	0	30	0	187	8	5	62.5%	2.7%
Africa	Southern	Zambia-2 2007	228	193	0	6	4	203	18	15	83.3%	7.4%
Africa	Southern	Zambia-3 2007	116	76	0	10	0	86	9	6	66.7%	7.0%
Africa	Southern	Zimbabwe-1 2008	230	215	0	4	0	219	15	12	80.0%	5.5%
		Southern Africa	1710	1234	2	168	5	1409	90	66	73.3%	4.7%
Africa	Western/Central	Cameroon-1 2009	141	76	0	47	0	123	6	4	66.7%	3.3%
Africa	Western/Central	Nigeria-1 2008	140	90	0	43	0	133	11	6	54.5%	4.5%
Africa	Western/Central	Nigeria-2 2008	143	83	0	54	0	137	13	13	100.0%	9.5%
Africa	Western/Central	Nigeria-3 2008	208	150	1	40	0	191	17	12	70.6%	6.3%
		Western/Central Africa	632	399	1	184	0	584	47	35	74.5%	6.0%
		Africa	4365	2964	3	541	11	3519	239	166	69.5%	4.7%
South-East Asia		India-1 2007	141	87	0	28	0	115	10	9	90.0%	7.8%
South-East Asia		India-2 2008	148	104	0	19	1	124	13	12	92.3%	9.7%
South-East Asia		Indonesia-1 2008	110	64	0	11	1	76	7	7	100.0%	9.2%
		South-East Asia	399	255	0	58	2	315	30	28	93.3%	8.9%
Overall			4764	3219	3	599	13	3834	269	194	72.1%	5.1%

Table 10 WHO acquired drug resistance survey: "HIV drug resistance prevention" outcome, by individual antiretroviral therapy clinic

WHO region	Subregion	Survey	People enrolled (A)	People on first-line ART at 12 months with viral load results classifiable (B)	Patients switching with viral load classifiable (C)	Lost to follow-up (D)	Stop ART (E)	Denominator for calculating outcomes (F: B+C+D+E)	Numerator: patients with viral load <1000 copies/ml at 12 months (G)	Outcome 1: HIV drug resistance prevention (G/F)
Africa	Eastern	Burundi-1 2007	125	108	0	1	0	109	92	84.4%
Africa	Eastern	Burundi-2 2007	136	105	0	3	0	108	87	80.6%
Africa	Eastern	Kenya-1 2007	221	173	0	17	0	190	157	82.6%
Africa	Eastern	Kenya-2 2008	223	183	0	10	1	194	167	86.1%
Africa	Eastern	Malawi-1 2006	148	51	0	24	5	80	48	60.0%
Africa	Eastern	Malawi-2 2006	143	77	0	28	0	105	71	67.6%
Africa	Eastern	Malawi-3 2006	145	90	0	20	0	110	87	79.1%
Africa	Eastern	Malawi-4 2006	160	52	0	7	0	59	49	83.1%
Africa	Eastern	Malawi-1 2008	153	111	0	9	0	120	102	85.0%
Africa	Eastern	Malawi-2 2008	150	83	0	20	0	103	77	74.8%
Africa	Eastern	Malawi-3 2008	150	94	0	26	0	120	88	73.3%
Africa	Eastern	Malawi-4 2008	150	107	0	12	0	119	99	83.2%
Africa	Eastern	Mozambique-1 2007	119	97	0	12	0	109	87	79.8%
		Eastern Africa	2023	1331	0	189	6	1526	1211	79.4%
Africa	Southern	South Africa-1 2007	224	170	1	13	0	184	157	85.3%
Africa	Southern	South Africa-2 2007	205	150	1	12	1	164	136	82.9%
Africa	Southern	South Africa-3 2007	208	153	0	18	0	171	147	86.0%
Africa	Southern	Swaziland-1 2008	133	62	0	27	0	89	55	61.8%
Africa	Southern	Swaziland-2 2008	127	58	0	48	0	106	53	50.0%
Africa	Southern	Zambia-1 2007	239	157	0	30	0	187	146	78.1%
Africa	Southern	Zambia-2 2007	228	193	0	6	4	203	173	85.2%
Africa	Southern	Zambia-3 2007	116	76	0	10	0	86	67	77.9%
Africa	Southern	Zimbabwe-1 2008	230	215	0	4	0	219	198	90.4%
		Southern Africa	1710	1234	2	168	5	1409	1132	80.3%
Africa	Western/Central	Cameroon-1 2009	141	76	0	47	0	123	69	56.1%
Africa	Western/Central	Nigeria-1 2008	140	90	0	43	0	133	79	59.4%
Africa	Western/Central	Nigeria-2 2008	143	83	0	54	0	137	70	51.1%
Africa	Western/Central	Nigeria-3 2008	208	150	1	40	0	191	132	69.1%
		Western/Central Africa	632	399	1	184	0	584	350	59.9%
		Africa	4365	2964	3	541	11	3519	2693	76.5%
South-East Asia		India-1 2007	141	87	0	28	0	115	77	67.0%
South-East Asia		India-2 2008	148	104	0	19	1	124	91	73.4%
South-East Asia		Indonesia-1 2008	110	64	0	11	1	76	57	75.0%
		South-East Asia	399	255	0	58	2	315	225	71.4%
Overall			4764	3219	3	599	13	3834	2918	76.1%

Table 11 WHO acquired drug resistance survey: "HIV drug resistance possible" outcome, by individual antiretroviral therapy clinic

WHO Region	Subregion	Survey	People enrolled (A)	People receiving first-line antiretroviral therapy at 12 months with viral load results classifiable (B)	People switching with viral load classifiable (C)	Lost to follow-up (D)	Stopped ART (E)	Denominator for outcome 3 (F: B+C+D+E)	Viral load >1000 copies/ml and wild type (G)	Viral load >1000 copies/ml, genotype fail (H)	Numerator of outcome 3 (I: D+E+G+H)	Outcome 3: HIV drug resistance possible (I/F)
Africa	Eastern	Burundi-1 2007	125	108	0	1	0	109	9	4	14	12.8%
Africa	Eastern	Burundi-2 2007	136	105	0	3	0	108	13	0	16	14.8%
Africa	Eastern	Kenya-1 2007	221	173	0	17	0	190	7	4	28	14.7%
Africa	Eastern	Kenya-2 2008	223	183	0	10	1	194	0	8	19	9.8%
Africa	Eastern	Malawi-1 2006	148	51	0	24	5	80	1	0	30	37.5%
Africa	Eastern	Malawi-2 2006	143	77	0	28	0	105	1	0	29	27.6%
Africa	Eastern	Malawi-3 2006	145	90	0	20	0	110	0	0	20	18.2%
Africa	Eastern	Malawi-4 2006	160	52	0	7	0	59	1	0	8	13.6%
Africa	Eastern	Malawi-1 2008	153	111	0	9	0	120	2	0	11	9.2%
Africa	Eastern	Malawi-2 2008	150	83	0	20	0	103	1	0	21	20.4%
Africa	Eastern	Malawi-3 2008	150	94	0	26	0	120	2	1	29	24.2%
Africa	Eastern	Malawi-4 2008	150	107	0	12	0	119	0	0	12	10.1%
Africa	Eastern	Mozambique-1 2007	119	97	0	12	0	109	0	1	13	11.9%
		Eastern Africa	2023	1331	0	189	6	1526	37	18	250	16.4%
Africa	Southern	South Africa-1 2007	224	170	1	13	0	184	5	2	20	10.9%
Africa	Southern	South Africa-2 2007	205	150	1	12	1	164	4	0	18	11.0%
Africa	Southern	South Africa-3 2007	208	153	0	18	0	171	1	4	23	13.5%
Africa	Southern	Swaziland-1 2008	133	62	0	27	0	89	1	0	28	31.5%
Africa	Southern	Swaziland-2 2008	127	58	0	48	0	106	1	0	49	46.2%
Africa	Southern	Zambia-1 2007	239	157	0	30	0	187	3	3	36	19.3%
Africa	Southern	Zambia-2 2007	228	193	0	6	4	203	3	2	15	7.4%
Africa	Southern	Zambia-3 2007	116	76	0	10	0	86	3	0	13	15.1%
Africa	Southern	Zimbabwe-1 2008	230	215	0	4	0	219	3	2	9	4.1%
		Southern Africa	1710	1234	2	168	5	1409	24	13	211	15.0%
Africa	Western/Central	Cameroon-1 2009	141	76	0	47	0	123	2	1	50	40.7%
Africa	Western/Central	Nigeria-1 2008	140	90	0	43	0	133	5	0	48	36.1%
Africa	Western/Central	Nigeria-2 2008	143	83	0	54	0	137	0	0	54	39.4%
Africa	Western/Central	Nigeria-3 2008	208	150	1	40	0	191	5	2	47	24.6%
		Western/Central Africa	632	399	1	184	0	584	12	3	199	34.1%
		Africa	4365	2964	3	541	11	3519	73	34	660	18.8%
South-East Asia		India-1 2007	141	87	0	28	0	115	1	0	29	25.2%
South-East Asia		India-2 2008	148	104	0	19	1	124	1	0	21	16.9%
South-East Asia		Indonesia-1 2008	110	64	0	11	1	76	0	0	12	15.8%
		South-East Asia	399	255	0	58	2	315	2	0	62	19.7%
Overall			4764	3219	3	599	13	3834	75	34	722	18.8%

Table 12 Distribution of subtypes by country among people initiating antiretroviral therapy in WHO acquired drug resistance surveys

Country and region	A	C	CRF01	CRF02	CRF06	CRF16	D	G	Other[a]	Total
Burundi	32	200	—	—	—	—	4	1	2	239
Kenya	277	54	—	—	—	26	56	5	—	418
Malawi	1	558	—	—	—	—	3	3	—	565
Mozambique	—	99	—	—	—	—	1	—	—	100
Eastern Africa	310	911	—	—	—	26	64	9	2	1322
South Africa	2	578	—	1	—	1	2	—	6	590
Swaziland	—	249	—	—	—	1	—	—	—	250
Zambia	3	519	—	3	—	—	1	3	2	531
Zimbabwe	3	1374	—	—	—	—	1	1	—	1379
Southern Africa	8	2720	—	4	—	2	4	4	8	2750
Cameroon	20	—	—	89	—	—	7	5	16	137
Nigeria	11	3	—	235	26	—	5	177	4	461
Western/Central Africa	31	3	—	324	26	—	12	182	20	598
Africa	349	3634	—	328	26	28	80	195	30	4670
India	1	285	—	—	—	—	—	—	—	286
Indonesia	—	1	108	1	—	—	—	—	—	110
South-East Asia	1	286	108	1	—	—	—	—	—	396
Overall	350	3920	108	329	26	28	80	195	30	5066

a Other subtypes with fewer than 10 specimens each: B, CRF09, CRF11, CRF13, F, H and K.

Table 13 Predicted drug resistance among people experiencing failure of first-line antiretroviral therapy at 12 months, by individual clinic

WHO Region	Subregion	Survey	n	AZT	d4T	FTC/3TC	TDF	ABC	ddI	Any NRTI	NVP	EFV	ETR	RPV	Any NNRTI	NRTI and NNRTI	Any PI	Any drug
Africa	Eastern	Burundi-1 2007	12	—	—	16.7%	—	16.7%	—	16.7%	25.0%	25.0%	16.7%	16.7%	25.0%	16.7%	8.3%	25.0%
Africa	Eastern	Burundi-2 2007	18	5.6%	5.6%	27.8%	—	27.8%	11.1%	27.8%	27.8%	27.8%	11.1%	16.7%	27.8%	27.8%	5.6%	27.8%
Africa	Eastern	Kenya-1 2007	8	—	—	75.0%	—	75.0%	12.5%	75.0%	100.0%	100.0%	25.0%	25.0%	100.0%	75.0%	—	100.0%
Africa	Eastern	Kenya-2 2008	12	8.3%	8.3%	25.0%	—	33.3%	16.7%	33.3%	33.3%	33.3%	8.3%	8.3%	33.3%	25.0%	—	41.7%
Africa	Eastern	Malawi-1 2006	3	—	—	66.7%	—	66.7%	33.3%	66.7%	66.7%	66.7%	33.3%	33.3%	66.7%	66.7%	—	66.7%
Africa	Eastern	Malawi-2 2006	6	—	—	33.3%	—	33.3%	16.7%	33.3%	83.3%	83.3%	83.3%	83.3%	83.3%	33.3%	—	83.3%
Africa	Eastern	Malawi-3 2006	3	—	33.3%	100.0%	33.3%	100.0%	33.3%	100.0%	100.0%	100.0%	66.7%	66.7%	100.0%	100.0%	—	100.0%
Africa	Eastern	Malawi-4 2006	3	—	—	66.7%	—	66.7%	—	66.7%	66.7%	66.7%	66.7%	66.7%	66.7%	66.7%	—	66.7%
Africa	Eastern	Malawi-1 2008	9	11.1%	11.1%	77.8%	11.1%	77.8%	33.3%	77.8%	66.7%	66.7%	44.4%	44.4%	66.7%	66.7%	—	77.8%
Africa	Eastern	Malawi-2 2008	6	—	—	50.0%	—	50.0%	—	50.0%	83.3%	83.3%	33.3%	33.3%	83.3%	50.0%	—	83.3%
Africa	Eastern	Malawi-3 2008	5	—	20.0%	60.0%	20.0%	60.0%	20.0%	60.0%	60.0%	60.0%	—	—	60.0%	60.0%	20.0%	60.0%
Africa	Eastern	Malawi-4 2008	8	—	25.0%	75.0%	25.0%	75.0%	62.5%	75.0%	100.0%	100.0%	75.0%	75.0%	100.0%	75.0%	—	100.0%
Africa	Eastern	Mozambique-1 2007	9	11.1%	22.2%	100.0%	22.2%	100.0%	44.4%	100.0%	100.0%	100.0%	88.9%	88.9%	100.0%	100.0%	—	100.0%
		Eastern Africa	102	3.9%	8.8%	52.0%	6.9%	52.9%	20.6%	52.9%	61.8%	61.8%	36.3%	37.3%	61.8%	51.0%	2.9%	63.7%
Africa	Southern	South Africa-1 2007	12	8.3%	16.7%	58.3%	16.7%	58.3%	25.0%	58.3%	58.3%	58.3%	25.0%	25.0%	58.3%	58.3%	41.7%	58.3%
Africa	Southern	South Africa-2 2007	14	—	21.4%	57.1%	14.3%	57.1%	35.7%	57.1%	71.4%	71.4%	14.3%	21.4%	71.4%	57.1%	14.3%	71.4%
Africa	Southern	South Africa-3 2007	2	—	—	50.0%	—	50.0%	50.0%	50.0%	50.0%	50.0%	—	—	50.0%	50.0%	—	50.0%
Africa	Southern	Swaziland-1 2008	7	14.3%	28.6%	71.4%	28.6%	71.4%	28.6%	71.4%	85.7%	85.7%	—	—	85.7%	71.4%	14.3%	85.7%
Africa	Southern	Swaziland-2 2008	5	60.0%	60.0%	80.0%	40.0%	80.0%	80.0%	80.0%	80.0%	80.0%	40.0%	40.0%	80.0%	80.0%	—	80.0%
Africa	Southern	Zambia-1 2007	8	—	50.0%	50.0%	37.5%	50.0%	50.0%	50.0%	62.5%	62.5%	50.0%	62.5%	62.5%	50.0%	12.5%	62.5%
Africa	Southern	Zambia-2 2007	18	5.6%	33.3%	72.2%	27.8%	72.2%	44.4%	72.2%	83.3%	83.3%	72.2%	72.2%	83.3%	72.2%	27.8%	83.3%
Africa	Southern	Zambia-3 2007	9	—	22.2%	55.6%	22.2%	55.6%	22.2%	55.6%	55.6%	55.6%	33.3%	33.3%	55.6%	44.4%	33.3%	66.7%
Africa	Southern	Zimbabwe-1 2008	15	26.7%	20.0%	73.3%	13.3%	73.3%	26.7%	73.3%	60.0%	60.0%	40.0%	46.7%	60.0%	53.3%	13.3%	80.0%
		Southern Africa	90	11.1%	27.8%	64.4%	22.2%	64.4%	36.7%	64.4%	68.9%	68.9%	36.7%	40.0%	68.9%	60.0%	21.1%	73.3%
Africa	Western/Central	Cameroon-1 2009	6	—	—	66.7%	—	66.7%	33.3%	66.7%	66.7%	66.7%	33.3%	33.3%	66.7%	66.7%	—	66.7%
Africa	Western/Central	Nigeria-1 2008	11	9.1%	18.2%	36.4%	—	36.4%	18.2%	45.5%	54.5%	54.5%	27.3%	27.3%	54.5%	45.5%	72.7%	54.5%
Africa	Western/Central	Nigeria-2 2008	13	23.1%	38.5%	84.6%	30.8%	84.6%	46.2%	84.6%	100.0%	100.0%	76.9%	76.9%	100.0%	84.6%	7.7%	100.0%
Africa	Western/Central	Nigeria-3 2008	17	5.9%	11.8%	64.7%	11.8%	64.7%	29.4%	64.7%	70.6%	70.6%	64.7%	64.7%	70.6%	64.7%	5.9%	70.6%
		Western/Central Africa	47	10.6%	19.1%	63.8%	12.8%	63.8%	31.9%	66.0%	74.5%	74.5%	55.3%	55.3%	74.5%	66.0%	21.3%	74.5%
		Africa	239	7.9%	18.0%	59.0%	13.8%	59.4%	28.9%	59.8%	66.9%	66.9%	40.2%	41.8%	66.9%	57.3%	13.4%	69.5%
South-East Asia		India-1 2007	10	30.0%	30.0%	80.0%	20.0%	80.0%	30.0%	90.0%	80.0%	80.0%	40.0%	50.0%	80.0%	80.0%	—	90.0%
South-East Asia		India-2 2008	13	23.1%	23.1%	69.2%	15.4%	69.2%	30.8%	69.2%	92.3%	92.3%	53.8%	53.8%	92.3%	69.2%	7.7%	92.3%
South-East Asia		Indonesia-1 2008	7	42.9%	57.1%	100.0%	28.6%	100.0%	57.1%	100.0%	100.0%	100.0%	85.7%	100.0%	100.0%	100.0%	—	100.0%
		South-East Asia	30	30.0%	33.3%	80.0%	20.0%	80.0%	36.7%	83.3%	90.0%	90.0%	56.7%	63.3%	90.0%	80.0%	3.3%	93.3%
Overall			269	10.4%	19.7%	61.3%	14.5%	61.7%	29.7%	62.5%	69.5%	69.5%	42.0%	44.2%	69.5%	59.9%	12.3%	72.1%

Table 14 Prevalence of drug resistance-associated mutations at treatment failure (12 months), by individual clinic

WHO Region	Subregion	Survey	n	K65R	D67N	K70R	M184IV	T215 any	K219 any	Any NRTI drug resistance mutation	Any TAM	K101E	K103NS	V106AM	Y181 any	Y188 any	G190 any	Any NNRTI drug resistance mutation	NRTI and NNRTI	Any drug resistance mutation
Africa	Eastern	Burundi-1 2007	12	—	—	—	16.7%	—	—	16.7%	—	—	16.7%	—	16.7%	—	—	25.0%	16.7%	25.0%
Africa	Eastern	Burundi-2 2007	18	—	5.6%	5.6%	27.8%	—	—	27.8%	5.6%	5.6%	11.1%	5.6%	5.6%	5.6%	5.6%	27.8%	27.8%	27.8%
Africa	Eastern	Kenya-1 2007	12	—	—	—	25.0%	—	—	33.3%	8.3%	—	33.3%	—	—	—	—	33.3%	25.0%	41.7%
Africa	Eastern	Kenya-2 2008	8	—	—	—	75.0%	—	—	75.0%	12.5%	—	62.5%	12.5%	25.0%	—	12.5%	100.0%	75.0%	100.0%
Africa	Eastern	Malawi-1 2006	3	—	—	—	66.7%	—	—	66.7%	33.3%	—	—	33.3%	33.3%	—	66.7%	66.7%	66.7%	66.7%
Africa	Eastern	Malawi-2 2006	6	—	—	—	33.3%	—	—	33.3%	—	16.7%	16.7%	16.7%	66.7%	16.7%	16.7%	83.3%	33.3%	83.3%
Africa	Eastern	Malawi-3 2006	3	33.3%	—	—	100.0%	—	—	100.0%	—	—	33.3%	—	66.7%	—	33.3%	100.0%	100.0%	100.0%
Africa	Eastern	Malawi-4 2006	3	—	—	—	66.7%	—	—	66.7%	—	—	—	—	66.7%	—	—	66.7%	66.7%	66.7%
Africa	Eastern	Malawi-1 2008	9	11.1%	—	—	77.8%	11.1%	11.1%	77.8%	11.1%	11.1%	33.3%	—	44.4%	—	11.1%	66.7%	66.7%	77.8%
Africa	Eastern	Malawi-2 2008	6	—	—	—	50.0%	—	—	50.0%	—	—	50.0%	—	33.3%	—	—	83.3%	50.0%	83.3%
Africa	Eastern	Malawi-3 2008	5	20.0%	—	—	60.0%	—	—	60.0%	—	—	60.0%	20.0%	—	—	—	60.0%	60.0%	60.0%
Africa	Eastern	Malawi-4 2008	8	25.0%	37.5%	—	62.5%	—	—	75.0%	37.5%	—	50.0%	12.5%	75.0%	12.5%	12.5%	100.0%	75.0%	100.0%
Africa	Eastern	Mozambique-1 2007	9	22.2%	—	11.1%	88.9%	—	11.1%	100.0%	22.2%	11.1%	22.2%	22.2%	77.8%	11.1%	22.2%	100.0%	100.0%	100.0%
		Eastern Africa	102	6.9%	3.9%	2.0%	50.0%	1.0%	2.0%	52.9%	9.8%	3.9%	29.4%	7.8%	32.4%	3.9%	9.8%	61.8%	51.0%	63.7%
Africa	Southern	South Africa-1 2007	12	16.7%	8.3%	—	41.7%	8.3%	8.3%	58.3%	16.7%	8.3%	33.3%	16.7%	16.7%	—	16.7%	58.3%	58.3%	58.3%
Africa	Southern	South Africa-2 2007	14	14.3%	—	—	57.1%	—	—	57.1%	—	7.1%	28.6%	35.7%	7.1%	7.1%	28.6%	71.4%	57.1%	71.4%
Africa	Southern	South Africa-3 2007	2	—	—	—	50.0%	—	—	50.0%	—	—	—	50.0%	—	—	—	50.0%	50.0%	50.0%
Africa	Southern	Swaziland-1 2008	7	14.3%	14.3%	14.3%	71.4%	14.3%	14.3%	71.4%	14.3%	—	57.1%	14.3%	—	28.6%	—	85.7%	71.4%	85.7%
Africa	Southern	Swaziland-2 2008	5	—	20.0%	20.0%	80.0%	60.0%	20.0%	80.0%	60.0%	—	60.0%	—	40.0%	—	20.0%	80.0%	80.0%	80.0%
Africa	Southern	Zambia-1 2007	8	37.5%	—	—	25.0%	—	—	50.0%	—	12.5%	25.0%	12.5%	37.5%	12.5%	12.5%	62.5%	50.0%	62.5%
Africa	Southern	Zambia-2 2007	18	27.8%	—	5.6%	72.2%	—	5.6%	72.2%	11.1%	22.2%	27.8%	16.7%	44.4%	—	33.3%	83.3%	72.2%	83.3%
Africa	Southern	Zambia-3 2007	9	22.2%	—	—	55.6%	—	—	55.6%	—	—	11.1%	33.3%	11.1%	—	33.3%	55.6%	44.4%	66.7%
Africa	Southern	Zimbabwe-1 2008	15	6.7%	20.0%	26.7%	73.3%	6.7%	6.7%	73.3%	33.3%	26.7%	6.7%	6.7%	6.7%	20.0%	26.7%	60.0%	53.3%	80.0%
		Southern Africa	90	17.8%	6.7%	7.8%	60.0%	6.7%	5.6%	64.4%	14.4%	12.2%	26.7%	18.9%	20.0%	7.8%	23.3%	68.9%	60.0%	73.3%
Africa	Western/ Central	Cameroon-1 2009	6	—	—	—	66.7%	16.7%	—	66.7%	16.7%	16.7%	50.0%	—	—	16.7%	16.7%	66.7%	66.7%	66.7%
Africa	Western/ Central	Nigeria-1 2008	11	—	—	9.1%	36.4%	—	18.2%	45.5%	18.2%	—	27.3%	—	27.3%	—	9.1%	54.5%	45.5%	54.5%
Africa	Western/ Central	Nigeria-2 2008	13	23.1%	15.4%	23.1%	84.6%	7.7%	7.7%	84.6%	30.8%	15.4%	30.8%	7.7%	46.2%	7.7%	23.1%	100.0%	84.6%	100.0%
Africa	Western/ Central	Nigeria-3 2008	17	5.9%	5.9%	—	64.7%	5.9%	—	64.7%	11.8%	17.6%	17.6%	—	41.2%	5.9%	17.6%	64.7%	64.7%	64.7%
		Western/Central Africa	47	8.5%	6.4%	8.5%	63.8%	6.4%	6.4%	66.0%	19.1%	12.8%	27.7%	2.1%	34.0%	6.4%	17.0%	72.3%	66.0%	72.3%
		Africa	239	11.3%	5.4%	5.4%	56.5%	4.2%	4.2%	59.8%	13.4%	8.8%	28.0%	10.9%	28.0%	5.9%	16.3%	66.5%	57.3%	69.0%

Table 14 Prevalence of drug resistance-associated mutations at treatment failure (12 months), by individual clinic (cont.)

WHO Region	Subregion	Survey	n	K65R	D67N	K70R	M184IV	T215 any	K219 any	Any NRTI drug resistance mutation	Any TAM	K101E	K103NS	V106AM	Y181 any	Y188 any	G190 any	Any NNRTI drug resistance mutation	NRTI and NNRTI	Any drug resistance mutation
South-East Asia		India-1 2007	10	—	20.0%	10.0%	80.0%	20.0%	10.0%	90.0%	40.0%	20.0%	30.0%	—	20.0%	30.0%	30.0%	80.0%	80.0%	90.0%
South-East Asia		India-2 2008	13	—	23.1%	15.4%	69.2%	15.4%	7.7%	69.2%	23.1%	15.4%	53.8%	15.4%	38.5%	—	30.8%	92.3%	69.2%	92.3%
South-East Asia		Indonesia-1 2008	7	14.3%	14.3%	28.6%	85.7%	14.3%	14.3%	100.0%	42.9%	—	14.3%	—	71.4%	14.3%	14.3%	100.0%	100.0%	100.0%
		South-East Asia	30	3.3%	20.0%	16.7%	76.7%	16.7%	10.0%	83.3%	33.3%	13.3%	36.7%	6.7%	40.0%	13.3%	26.7%	90.0%	80.0%	93.3%
Total			269	10.4%	7.1%	6.7%	58.7%	5.6%	4.8%	62.5%	15.6%	9.3%	29.0%	10.4%	29.4%	6.7%	17.5%	69.1%	59.9%	71.7%

Note: Specimens with PR only genotypes available are excluded for the table.

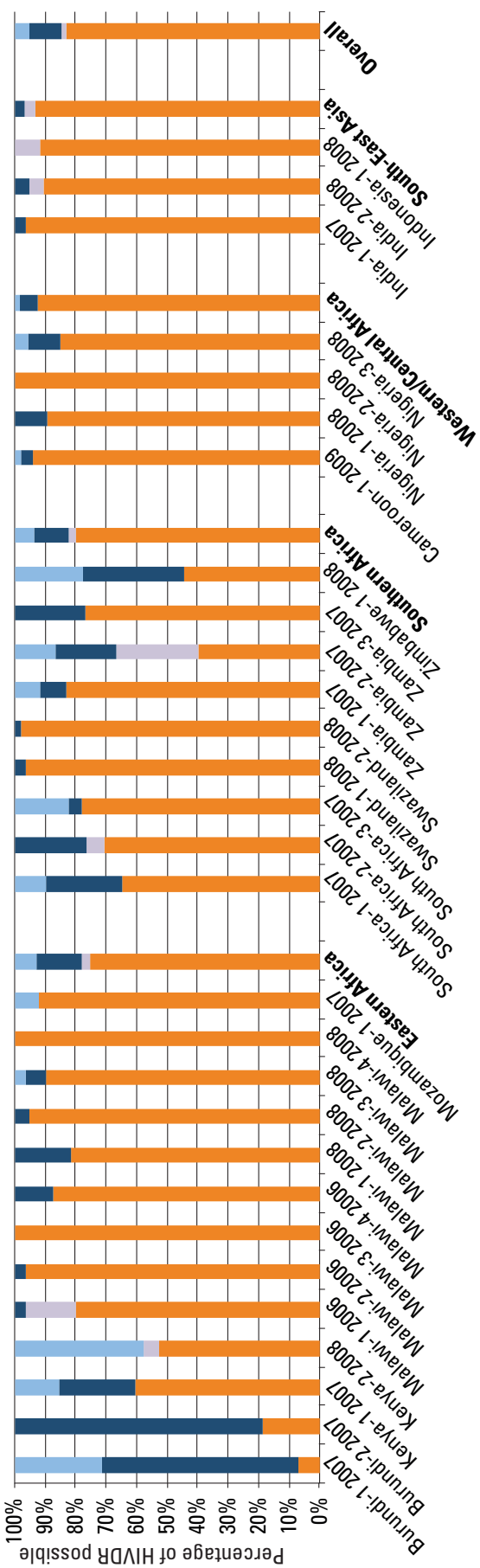
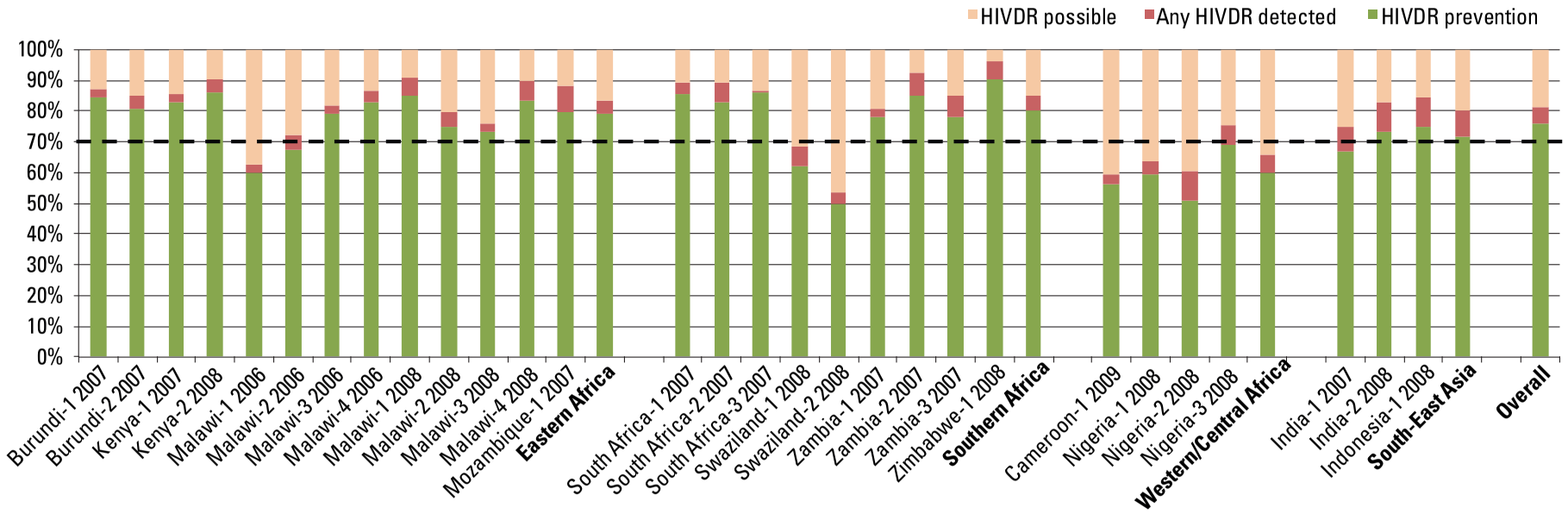


Figure 3 Breakdown of possible HIV drug resistance outcome, by individual clinic

Figure 4 The three outcomes of surveys of acquired HIV drug resistance, by antiretroviral therapy clinic



For more information, contact:

World Health Organization
Department of HIV/AIDS
20, avenue Appia
1211 Geneva 27
Switzerland

E-mail: hiv-aids@who.int

http://www.who.int/hiv/en/

ISBN 978 92 4 150393 8