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Chapter 17

Summary and general discussion

Sub-Saharan Africa is the region most heavily affected by HIV/AIDS worldwide [1]. Access to combination antiretroviral therapy (ART) has rapidly expanded during the past decade to reach millions of HIV-1 infected people in the region [1], which has dramatically reduced HIV-related morbidity and mortality [2]. To allow the ART scale-up, the WHO-recommended public health approach has been critical. This approach is based on simplified treatment protocols, including standard first-line and second-line ART regimens, limited laboratory monitoring, and a decentralized service delivery [1]. Recommended first-line regimens combine a dual nucleos(t)ide reverse transcriptase inhibitor (NRTI) backbone with a non-NRTI (NNRTI). Recommended second-line regimens include two new or recycled NRTIs and a ritonavir-boosted protease inhibitor (bPI). Because of resource constraints, routine plasma viral load (pVL) monitoring to detect and manage ART failure is generally not feasible. Instead, ART failure is commonly diagnosed using WHO-defined clinical criteria and –if available– CD4 cell counts [1]. To date, relatively little attention has been paid to the potential emergence and spread of drug-resistant HIV-1 and its public health implications after the introduction of large-scale ART programs in the region.

Obstacles to universal and sustained ART access include weak ART program functioning, lack of sustainable long-term funding, and human resource constraints. An inevitable consequence of ART scale-up is treatment failure that selects for drug-resistant HIV-1 (acquired drug resistance). Such virus has the potential to limit the response to subsequent treatment and can be transmitted to newly infected individuals (transmitted drug resistance, TDR). Although the ART rollout in sub-Saharan Africa has employed (potent) triple combination therapy, the emergence of drug resistance could be exacerbated because of several reasons. Factors contributing to emerging drug resistance include suboptimal long-term adherence [3], lack of pVL monitoring [4, 5], treatment interruptions due to drug stockouts [6], drug-drug interactions [7] and the use of substandard regimens, including single-dose nevirapine for prevention of mother-to-child HIV transmission (PMTCT) [8]. Concern has been raised about rising drug-resistant HIV-1 in resource-limited countries as a potential threat to the worldwide control of HIV/AIDS [9].

To address the issue of HIV-1 drug resistance in resource-limited settings, a collaborative bi-regional program was established in the African and Asian-Pacific regions in 2006, entitled *Linking African and Asian Societies for an Enhanced Response to HIV/AIDS* (denoted LAASER). LAASER aimed to develop the regional capacities for the population-level assessment of acquired and transmitted HIV-1 resistance, funded by The Netherlands Ministry of Foreign Affairs in partnership with Stichting AidsFonds (2006-2011). As part of LAASER, the *PharmAccess African Studies to Evaluate Resistance* (PASER) network was established as a collaborative partnership of clinical sites, laboratories and research

groups in Kenya, Nigeria, South Africa, Uganda, Zambia, and Zimbabwe. To address the challenges associated with the high costs and complexity of HIV-1 genotypic resistance testing, PASER initiated a public–private consortium, called *Affordable Resistance Test for Africa* (ART-A), which aims to develop simplified, more affordable test algorithms for HIV-1 drug resistance.

This thesis is dedicated to clinical, epidemiological and public health studies related to HIV-1 drug resistance in sub-Saharan Africa, which were conducted as part of the PASER and ART-A programs. The aims of the studies described in the thesis were to define the epidemiology of TDR in HIV-1 infected populations in sub-Saharan Africa after the scale-up of ART, to assess the effects of pre-therapy resistance on the response to first-line or second-line ART, to assess patterns of drug-resistance mutations (DRMs) and their clinical impact in patients experiencing failure of standard first-line or second-line ART, and to explore the implications of emerging HIV-1 drug-resistance for public health policy in resource-limited countries.

As an introduction to the thesis, we reviewed the available data on HIV-1 drug resistance in sub-Saharan Africa before the start of the PhD research (before 2008) (**Chapter 2**), including an illustrative patient case study (**Chapter 3**). Early studies on TDR and acquired resistance are limited in number and quality, because of small and selected patient samples as well as heterogeneity across study designs, populations and time periods. In **Chapter 4**, we profiled the PASER-Monitoring (PASER-M) cohort. This multicentre observational cohort comprises a total of 2985 HIV-1 infected adults starting first-line or second-line ART, who were enrolled at 13 clinical sites in the abovementioned countries between March 2007 and September 2009 and followed up prospectively.

PART I: TRANSMITTED HIV-1 DRUG-RESISTANCE

In Europe and North America, HIV-1 drug-resistance has initially been driven by sequential non-potent mono and dual therapies of nucleoside reverse-transcriptase inhibitors (NRTIs) in the early days of HIV/AIDS treatment, leading to high levels of acquired resistance in treated individuals in the 1990s. This was associated with high levels of TDR, peaking in some settings at over 20% before levelling off at between 9-15% more recently [10-13]. Recent stabilizing or declining levels of TDR in resource-rich countries are likely attributed to declining incidence of acquired resistance, due to the use of more potent ART regimens, regimen individualization by use of pre-therapy resistance testing, and close pVL monitoring [14]. It has been difficult to predict TDR trends for sub-Saharan Africa after the ART scale-up based on the experiences from resource-rich

countries, given that the histories of antiretroviral drug access and the health system conditions differ significantly between these settings [15-17]. Mathematical modelling of TDR in Africa, attempted to inform public-health strategies, has yielded conflicting results. For instance, one study predicted low rates of TDR (<5%) until 2015 [18], whilst another study, based on the Botswana ART program, predicted that TDR could reach 15% by 2009 if acquired resistance rates were high [19, 20]. These discordant findings highlight the importance of timely and accurate empirical data.

In **Chapter 5**, we compared pre-therapy drug resistance between antiretroviral-naïve (n=523) and antiretroviral-exposed (n=25) persons, who were about to start standard first-line ART at either of three clinical sites in Lusaka, Zambia [21]. 5% of the study population reported previous antiretroviral exposure, either as ART, single-dose nevirapine for PMTCT, combination therapy for PMTCT, or unspecified. The main finding was that drug-resistant HIV-1 was detected in 16.0% of patients who were antiretroviral-exposed, compared with 5.2% of antiretroviral-naïve patients (p=0.022). Pre-therapy DRM patterns and frequencies did not differ between an established private versus two recently introduced free ART programs.

In **Chapter 6**, we reported that, overall, 5.6% of 2436 antiretroviral-naïve individuals from 11 areas in Kenya, Nigeria, South Africa, Uganda, Zambia and Zimbabwe harboured TDR, which was mostly NNRTI-associated and limited to a single drug-class [22]. The prevalence of TDR in antiretroviral-naive individuals appeared substantially higher in Uganda (12%), where antiretroviral drugs were available at least five years ahead of the nearby countries, compared with the other five countries (<5%). TDR was estimated to increase with time since the start of the ART roll-out, by –on average– 38% (95%CI 13-68; p=0.01) per year. For NNRTI-resistance, the increase was estimated at 35% (95%CI 1-81; p=0.041) per year.

In **Chapter 7**, we reported a TDR prevalence of 8.6% (95%CI 3.2–17.7) among 70 recently HIV-1 infected attendees at voluntary counseling and testing sites in Kampala, Uganda, in 2009, which was ten years after the local ART roll-out [23]. This estimate was likely to represent an increase compared to the previous survey in 2006–2007 that did not detect any DRMs among 47 recently infected pregnant women [24]. This study was among the first to suggest an increase in TDR between repeated surveys within the same geographic area in Africa, although the subsequent surveys targeted different subpopulations.

The PASER-M cohort is one of the largest studies on the topic of HIV-1 drug-resistance to date. An important strength of the study was the large number of patients and sites participating, representing a diverse spectrum of patient populations, clinic types, ART

regimens and HIV-1 subtypes. However, although the PASER network was designed to geographically represent the African sub-regions, the generalizability of the study was limited by the fact that only six countries were included and that the collaborating clinical sites were not selected randomly. To enable a more comprehensive description of regional TDR time trends, PASER has collaborated in a WHO-initiated meta-analysis of all available TDR studies [25]. Of the 218 datasets comprising 26,102 untreated patients from 42 countries, PASER accounted for 9% of all patients and 17% of patients from sub-Saharan Africa. The meta-analysis demonstrated an increasing prevalence of TDR in the east and southern African sub-regions. East Africa had the highest estimated rate of increase at 29% per year (95%CI 15-45, p=0.0001) since roll-out, with an estimated prevalence of TDR at eight years post-roll-out (circa 2011) of 7.4% (95%CI 4.3-12.7). The increase in southern and West/Central Africa was 14% (95%CI 0-29, p=0.054) and 3% (95%CI -0.9-16, p=0.618) per year respectively. There were substantial increases in NNRTI resistance in east Africa [36% per year (95%CI 21-52, p<0.0001)] and southern Africa [(23% per year, 95%CI 7-42%, p=0.0049)]. Rising TDR levels have also been reported in recent studies among newly infected populations from east [26], central [27] and southern Africa [26]. These data corroborate the PASER findings reported in **Chapters 6 and 7**, adding to the increasingly convincing evidence that the scale-up of ART in Africa is driving a rise in TDR, particularly associated with NNRTIs. The rise in NNRTI resistance is of particular concern, as this drug class constitutes the foundation of currently recommended first-line ART and PMTCT regimens [28, 29]. Repeated surveys in the same and other settings and subpopulations are urgently needed to evaluate the evolution of TDR over time.

There is ongoing debate on what is the most appropriate target population to conduct TDR surveys, i.e. either recently infected persons or pre-therapy patients at ART initiation. Recently infected populations would maximize the detection of true TDR mutations, and minimize the contribution of acquired resistance due to prior antiretroviral exposure, thus enabling reliable analyses of TDR time trends. However, there are significant challenges in identifying individuals during recent HIV-1 infection. For instance, TDR surveys among newly diagnosed populations at antenatal care clinics or voluntary counseling and testing sites –who are likely to be recently infected– are logistically complex and require a high screen load, thus limiting their feasibility especially in low-prevalence settings. This has also been our experience in conducting the PASER-S surveys. By contrast, in pre-therapy populations (such as in PASER-M), who are easy to sample at ART sites, the prevalence of true TDR may be underestimated due to reversion [30], and TDR reflects past ART availability at the population-level. Moreover, there is a risk of contributing acquired resistance due to (undisclosed) prior antiretroviral exposure. Nevertheless, from a public health perspective, it must be recognized that pre-therapy

resistance, whether due to transmission or undisclosed prior antiretroviral exposure, will both impact adversely on the response to national ART programs. Furthermore, TDR survey results from pre-therapy populations will be directly applicable to inform current ART guidelines. Therefore, given the abovementioned feasibility issues and the restricted resources that are currently available for HIV-1 drug resistance surveillance, we here argue that surveying pre-therapy resistance in populations at ART initiation should be prioritized. Where feasible, surveying TDR in newly infected populations, if conducted sequentially, will provide important additional information to guide drug-resistance prevention strategies in ART programs and to inform future ART guidelines.

PART II: ANTIRETROVIRAL TREATMENT AND ACQUIRED DRUG-RESISTANCE

In Europe and North America, pre-therapy resistance testing is routinely performed to guide first-line ART choices [31, 32], which has been shown to mitigate virological failure in persons with TDR [33]. By contrast, in resource-limited countries, drug resistance testing is not routinely available and WHO-recommended first-line and second-line ART regimens are empirically prescribed. In **Chapter 8**, we reported that among 2733 PASER-M participants who had received one year of standard first-line NNRTI-based ART, the presence of pre-therapy resistance more than doubled the risk of virological failure and the further acquisition of DRMs, in those patients who received partly-active regimens — i.e., that included at least one drug to which the virus had reduced susceptibility [34]. These findings were largely in agreement with results from a large collaborative analysis in Europe [33]. Additionally, 70% of participants who had pre-therapy resistance were empirically started on a suboptimum first-line regimen — comprising nearly 5% of the total study population [34]. Given the low genetic barrier of NNRTI-based regimens, our study emphasized the need for at least three fully-active antiretroviral drugs in first-line regimens to ensure an optimum virological response and to prevent the further acquisition of resistance. Independently of pre-therapy resistance, we found that previous use of ART or PMTCT, failure to achieve an increase in CD4 cell count in the first six months of ART, and prolonged non-adherence below 95% were associated with virological failure and the further acquisition of resistance.

There is limited knowledge of DRMs in HIV-1 non-B subtypes and their clinical relevance, despite the fact that more than 90% of HIV-1 infections globally belong to non-B subtype variants [35]. In **Chapter 10**, we observed that among 250 patients at time of switch after prolonged first-line failure, in the absence of pVL monitoring, 88% had at least one DRM, including high frequencies of M184V and accumulated NRTI and NNRTI mutations [5]. Several studies in patients with late detection of ART failure have reported high fre-

quencies of accumulated NRTI and NNRTI mutations, including TAMs, K65R and Q151M, conferring broad cross-resistance [4, 5, 36-38]. In **Chapter 9**, we observed that among 142 patients who experienced virological failure after the first year of ART, 70% had at least one DRM, mostly M184V and NNRTI-associated [39]. Observed DRM patterns in both studies were more extensive than for cohorts that received close (three-monthly) pVL monitoring in South Africa [40] and resource-rich countries [41, 42]. Thus, these recent observational studies from the region corroborate the notion that routine pVL monitoring prevents accumulation of DRMs and preserves HIV susceptibility.

Recent studies have suggested increased rates of the K65R mutational pattern in subtype C, compared with subtype B, which may be due to the nature of the subtype C RNA template of the viral reverse transcriptase [43, 44]. By contrast, in subtype B, the generation of D67N and TAMs is facilitated instead of K65R [43, 44]. In our multi-country African study of mostly subtype A, C, or D infected persons, the K65R pattern was frequently selected after failure on stavudine (15%) or tenofovir (28%) containing first-line regimens (**Chapter 9**) [39]. This finding suggested that, after failure of a stavudine-containing first-line regimen, zidovudine rather than tenofovir (as recommended by the current WHO guidelines [28]), might be the preferred second-line NRTI in non-B subtype infected populations where stringent pVL monitoring is lacking. The data reported in **Chapters 9 and 10** also suggested that the second-generation NNRTIs etravirine or rilpivirine are unlikely to be effective as part of second-line ART, if combined with two NRTIs, given the high frequencies of Y181C and accumulated NNRTI mutations.

Few data are available on the extent of misdiagnosis of true virological failure using the common diagnostic approach that adopts clinical and/or immunological definitions of ART failure [45, 46]. In **Chapter 10**, we demonstrated that, in the absence of pVL testing, switches from first- to second-line ART occur unnecessarily in up to 50% of cases [5]. Assuming that second-line treatment is 2.3-fold more expensive than first-line (CHAI prices [47]), this means that for every patient who is switched to second-line unnecessarily, at least one other patient will be held back from accessing first-line ART. To further investigate this important finding, we conducted a cost-effectiveness analysis that attempted to quantify and compare the economic implications of different diagnostic strategies (**Chapter 14**).

In **Chapter 11**, we investigated the initial response to empiric second-line ART in 243 patients who experienced first-line failure [48]. In our cohort, we found that the risk of second-line ART failure was not increased in participants who carried a virus with predicted reduced susceptibility to at least one prescribed second-line drug, compared with those who received ART that was predicted to be fully-active. In addition to our study,

one study in Malawi has suggested that empiric bPI-based regimens can successfully re-suppress HIV-1 replication (in 85-86% of patients), despite the presence of extensive NRTI resistance [48, 49]. By contrast, the ACTG5230 trial, evaluating bPI monotherapy after first-line failure, found that about one third of patients who achieved <400 HIV-RNA c/ml after 24 weeks, appeared to have incomplete viral suppression at between 40-200 HIV-RNA c/ml [50]. Additionally, the randomized HIV Star Study in Thailand found that second-line bPI monotherapy was virologically inferior to triple therapy in patients failing NNRTI-based first-line (61% vs 83% HIV-RNA<50 c/ml) [51]. Thus, bPI monotherapy should not currently be recommended as second-line therapy, and large international trials are underway to further assess this issue.

A recent systematic review and meta-analysis of outcomes of patients on second-line ART in resource-limited settings showed that rates of virological failure are high (23%, 27% and 38% at 12, 24 and 36 months, respectively) and associated with duration of exposure to previous drug regimens and poor adherence, rather than resistance development to bPIs, which is likely attributable to their high genetic barrier to resistance [52]. Therefore, a major concern seems to be poor long-term adherence, especially given that therapeutic options beyond second-line are very expensive and largely non-existent in most African countries.

PART III: PUBLIC HEALTH POLICY

An effective public health framework is required to assess and contain HIV-1 drug-resistance in sub-Saharan Africa [53]. In **Chapter 12**, we reported practice-based lessons learned in the PASER network [54]. Through the assessment of resistance at site and regional levels, PASER has contributed to evidence-based recommendations to inform ART guidelines and to provide feedback on the effectiveness of HIV-1 treatment and prevention programs. The PASER network has contributed to the goals of the WHO Global HIV Drug Resistance Network (HIVResNet) [53]. The sustainability of the PASER network is challenged by funding limitations, the need for continued training and education, constraints in human resources, a persistently vulnerable general health infrastructure, and the urgent need for simplified and affordable diagnostic technology.

WHO recommends that ART programmatic factors, such as prescribing practices, patient retention and drug supply, which are associated with acquired drug resistance, are monitored to optimize the quality of patient care [53]. The minimum-resource WHO-defined early warning indicators (EWIs) make use of data that are routinely collected in patients' medical and pharmacy records. In **Chapter 13**, we reported the assessment

of the EWIs in the PASER network from 2007-2009. Eleven of 13 (85%) sites prescribed appropriate first-line ART regimens for all patients; 12 (92%) sites met the targets of ≤20% loss to follow-up and ≥70% pVL suppression; all sites achieved ≥70% retention on first-line ART. EWI assessment in the PASER network identified vulnerable aspects of ART programs and triggered programmatic interventions aimed at minimizing resistance development. Interestingly, a comprehensive WHO assessment of 907 ART programs in the region between 2004 and 2009 documented drug stock-outs in about 40% of sites, more than 20% of loss to follow-up in 40% of sites, and ART prescription congruent with national guidelines to 100% of patients in 74% of sites [55]. Important gaps in service delivery and program performance affect a considerable proportion of ART programs, particularly with respect to the fragility of procurement and supply systems and inadequate patient retention.

Previous evaluations have yielded conflicting results regarding the survival gains and cost-effectiveness associated with ART diagnostic strategies based on CD4 cell counts alone, or CD4 cell counts combined with pVL monitoring [56-58]. The benefits of routine pVL monitoring in avoiding unnecessary switches and resistance accumulation are increasingly being acknowledged (**Chapter 10**) [5]. Since any resources used to conduct laboratory testing could divert funds away from expanding access to ART, it is critical to establish the most cost-effective ART management strategies. In **Chapter 14**, we reported a Markov-based cost-effectiveness analysis, establishing that laboratory-based diagnostic strategies, using either CD4 cell counts or pVL, can provide substantial (15-30%) cost savings for long-term ART management in sub-Saharan Africa by averting the high costs of unnecessary switching to second-line therapy [59]. This model is the first cost-effectiveness analysis we know of to compare different diagnostic strategies for ART management that includes a "pVL only" strategy, without concomitant CD4 cell counts. pVL monitoring has the public health advantages of supporting adherence [60], and identifying patients at risk of developing resistance [61] or transmitting HIV [62]. Previous studies in developed countries have suggested that there is limited benefit from continued measurements of CD4 cell counts in patients who have achieved pVL suppression [63, 64]. Use of CD4 counts could thus be restricted to establish eligibility for ART initiation, and to determine the need for prophylaxis for opportunistic infections. Challenges to scaling-up pVL testing in Africa are surmountable, since recent technological advances enable lower test cost, simplified sample storage and shipment with the use of dried blood spots, as well as easy-to-maintain real-time PCR machines [65]. As the number of persons receiving ART rises and test prices go down, the potential health benefit and cost savings from the use of laboratory monitoring will further increase.

Dried spots on filter paper made of whole blood (dried blood spots; DBS), plasma (dried plasma spots; DPS) or serum hold promise as an economical and practical alternative specimen source to liquid plasma for pVL determination and drug resistance genotyping in resource-limited countries. In **Chapter 15**, we reviewed the evidence that was available up to 2009 for the utility of dried fluid spots for the determination of pVL and resistance genotyping. Available data indicated that pVL determination and resistance genotyping from DBS and DPS is feasible. Limitations included reduced analytical sensitivity resulting from small analyte volumes, nucleic acid degradation under environmental conditions, impaired efficiency of nucleic acid extraction, potential interference of archived proviral DNA in genotypes obtained from DBS and the excision of spots from the filters in high-volume testing. The current sensitivity in resistance testing is probably appropriate for public health surveillance among pre-therapy populations. The ART-A consortium and other groups are involved in ongoing research that aims to improve analytical sensitivity and assay conditions, in order to expand the routine application of DBS in public health surveillance as well as the therapeutic monitoring of individuals receiving ART.

In **Chapter 16**, we expounded a viewpoint that rising drug-resistant HIV-1 in sub-Saharan Africa is a potential threat to the worldwide control of HIV/AIDS. The highest priority remains achieving the goal of providing ART to 15 million people by 2015 worldwide. In addition to large health gains, the economic benefits of ART have been estimated to exceed program costs within ten years of investment [66]. The strengthening of national HIV treatment programs that include robust supply chains, improved access to (low-cost) pVL technologies, improved access to second and third-line regimens, and a population-based framework for resistance assessment are a global priority. Investment in such infrastructure now will be worthwhile in the medium to long term.

FUTURE PERSPECTIVES

Continued and increased international funding support remains essential to reach the goal of universal access and to improve the quality of HIV/AIDS treatment in sub-Saharan Africa. PASER, in conjunction with other studies, has provided compelling evidence that HIV-1 drug-resistance is emerging after the ART scale-up in sub-Saharan Africa, which represents a potential threat to the worldwide control of HIV/AIDS. To ensure continued effectiveness of HIV/AIDS treatment, ART guidelines in resource-limited countries should take into account the most recently available local, regional and global data on HIV-1 drug resistance.

There is ongoing debate on what should be the public health response to high levels of TDR in any given setting. There is not a clear-cut TDR level at which policy change is indicated in all settings. Potential options for public health interventions include a shift in standard first-line ART from NNRTI-based to bPI-based, the introduction of individual-level drug resistance testing before ART initiation, and the introduction of pVL monitoring for early failure detection. A shift to bPI-based ART as standard first-line therapy at current drug prices is generally considered the last resort by many experts, given that such a change would have major programmatic implications, substantially increase drug cost and seriously restrict options for constructing an effective second-line regimen with currently available drugs. Of note, the 2011 Clinton HIV/AIDS Foundation (CHAI) drug prices are US$169 per year for a recommended first-line regimen (tenofovir, lamivudine, efavirenz) and US$395 per year for a second-line regimen (atazanavir/ritonavir, tenofovir, lamivudine), which is a 2.3-fold cost difference [47]. Routine individualized pre-therapy resistance testing is not likely to become feasible for most ART programs in the region, because of serious constraints in laboratory capacity and financial resources. Implementing routine pVL monitoring seems a more feasible option. The accurate identification of patients who experience virological failure will preserve drug options by avoiding the incremental cost associated with unnecessary switching and by reducing drug resistance accumulation. Moreover, a recent model of HIV transmission predicted that TDR in resource-limited settings will be reduced if some form of pVL monitoring is introduced [67]. Mathematic modeling and economic analyses will be crucial to provide strategic information in establishing the most cost-effective use of diagnostic strategies and drugs and to determine funding priorities. In this respect, it should be noted that the level of TDR is only one factor in determining whether a policy change for ART programs will be cost-effective. Finally, based on our study findings, we can make the pragmatic recommendation that the accurate, routine screening of previous exposure to ART and PMTCT should be strengthened, and that for individuals who report previous use of (NNRTI-based) ART or PMTCT, bPI-based first-line ART, or at least intensified monitoring, should be considered.

Robust ART programmatic evaluation of site-level factors associated with acquired resistance can play an important role in identifying and addressing deficiencies in ART delivery. The WHO-defined EWIs should become integrated into routine ART program monitoring and evaluation systems. To make this feasible, the currently recommended set of EWI will need to be simplified and synchronized with existing indicators. Additionally, repeated population-level laboratory-based drug resistance surveys are imperative and should be routinely integrated in national HIV treatment programs. Extended capacity for quality-assured drug resistance testing is needed to facilitate the conduct of these surveys. Funders and national governments must step up to support and sustain

population-based drug resistance surveillance. Evidence-based information will serve as a powerful advocacy tool towards funding agencies and policy makers to advance the sustainability and quality of HIV/AIDS treatment.

Further research is needed to investigate optimal strategies to prolong the effective use of first-line ART regimens, and to investigate in what conditions bPI-based regimens may offer a feasible alternative to current first-line regimens in view of increasing TDR levels. Optimal strategies for ART sequencing need to be determined, including the long-term effectiveness of bPI-monotherapy, the impact of multidrug NRTI mutations on empiric bPI-based second-line regimens, and the possible role of new drug classes (e.g. integrase inhibitors, second-generation NNRTIs). Additionally, it needs to be established what is the most cost-effective pVL threshold for switching therapy, and what is the role of resistance genotyping in resource-limited countries.

Because of clinical benefits, international guidelines recommend earlier initiation of ART at CD4 <350 or even <500 cells/μl [28, 31]. As of recent, early treatment has attracted significant attention as a promising tool to reduce the number of people acquiring HIV infection [62]. Little is yet known on what will be the population effects of the widespread implementation of early treatment in sub-Saharan Africa, in terms of HIV prevention, survival and drug resistance development. Earlier ART initiation could be anticipated to lead to a further rise in TDR. It needs to be established whether this risk is outweighed by a reduction in the number of new HIV infections.

CONCLUSION

The introduction of large-scale HIV/AIDS treatment in sub-Saharan Africa less than a decade ago has saved millions of lives. There is now compelling evidence from PASER and other studies that HIV-1 drug-resistance is on the rise after the ART scale-up, which may restrict therapeutic options, increase mortality, and augment treatment costs. To date, substantial progress has been made in assessing the development and spread of drug-resistant HIV-1 and its potential public health implications. Concerted action by international agencies, national governments, ART programs and major funding agencies will be critical to identify and address programmatic challenges associated with drug resistance, and preserve the long-term effectiveness of available ART regimens in Africa. Greater funding, political will and infrastructure are required to sustain and expand global resistance surveillance efforts, in order to ensure responsible provision of life-long HIV/AIDS treatment. WHO, in conjunction with experts in the field, should step up in convincing the decision-makers in governments and funders of the urgency of

HIV-1 drug resistance as a possible threat to the success of the global HIV/AIDS control. Without continued and increased international efforts and funding support, emerging resistance has the potential to curb, and even reverse, further progress on breaking the HIV epidemic.

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