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# The quality of antiretroviral medicines: an uncertain problem

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## ABSTRACT

**Objectives** Substandard and falsified (SF) antiretrovirals (ARVs) risk poor outcomes and drug resistance, potentially affecting millions of people in need of treatment and prevention. We assessed the available evidence on SF ARV and related medical devices to discuss their potential public health impact.

**Methods** Searches were conducted in Embase, PubMed, Google, Google Scholar, Web of Science and websites with interest in ARV quality in English and French up to 30 November 2021. Publications reporting on the prevalence of SF ARV were assessed in a quantitative analysis using the Medicine Quality Assessment Reporting Guidelines (MEDQUARG).

**Results** We included 205 publications on SF ARV and 11 on SF medical devices. Nineteen prevalence surveys of SF ARV, published between 2003 and 2021, were included, with no surveys relevant to SF medical devices. The prevalence survey sample size ranged from 3 to 2630 samples (median (Q1–Q3): 16.0 (10.5–44.5); 3 (15.8%) used random outlet sampling methods. Of the 3713 samples included in the prevalence surveys, 1.4% (n=51) failed at least one test. Efavirenz, nevirapine and lamivudine-nevirapine-stavudine combination were the most surveyed ARV with failure frequencies of 3.6% (7/193), 2.6% (5/192) and 2.8% (5/177), respectively. The median (Q1%–Q3%) concordance with the MEDQUARG criteria was 42.3% (34.6%–55.8%).

**Conclusion** These results suggest that there are few data in the public domain of the quality of ARV in supply chains; the proportion of SF ARV is relatively low in comparison to other classes of essential medicines. Even a low proportion of the ARV supply chain being poor quality could make a large difference in the HIV/AIDS international landscape. The 95-95-95 target for 2026 and other international targets could be greatly hampered if even 1% of the millions of people taking ARV (for both prevention and prophylaxis) receive medicines that do not meet quality standards. More surveillance of SF ARV is needed to ensure issues are detected.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Substandard and falsified (SF) antiretrovirals (ARVs) lead to negative health impacts for patients with HIV infection, including poor patients outcomes and economic losses. They also likely to have global public health impact engendering drug resistance. However, data on SF ARV are scattered without global understanding of their epidemiology and impact.

### WHAT THIS STUDY ADDS

⇒ In the 19 studies, we identified that aimed to understand their epidemiology, 1.4% of the 3713 ARV samples failed at least one quality test.

⇒ However, this estimate is not generalisable globally due to major gaps in the evidence, with geographical disparities and survey methodology issues. Prevalence surveys mainly included ARV samples collected in Africa and we found no publicly available evidence for almost 90% of national states.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings suggest that SF ARV are a public health issue as even a low proportion of the ARV supply chain being poor quality could make a large difference for the millions of patients who take them globally.

⇒ More research with robust methodology and reporting is required to provide more precise estimates of the extent of the problem, where and what the problems are and the potential impact of SF ARV on drug resistance and patient outcome, to better inform interventions and policy.

## INTRODUCTION

Antiretrovirals (ARVs) are primarily used for the treatment and prevention of infection by the human immunodeficiency virus (HIV).[1] According to the WHO, approximately 38.4 million people were living with HIV at the end of 2021[2] and by July 2022, the HIV/AIDS had caused 40.1 million deaths globally.[2] Approximately 850 children became infected with HIV and approximately 310 children died each day in 2021 from AIDS-related causes.[3]

Globally, 75% of HIV-infected people were receiving antiretroviral therapy (ART) at the end of 2021.[2 4] With no cure or vaccine currently available, access to quality ART is crucial to control the infection and help prevent transmission. The WHO estimated that between 2000 and 2019 ARV saved

15.3 million lives and reduced the percentage of new HIV infections by 39% and HIV-related deaths by 51%.[5]

HIV drug resistance (HIVDR) affects the efficacy of ART, resulting in increased HIV-associated morbidity and mortality and transmission. According to surveys conducted in 10 countries in sub-Saharan Africa (2012–2020), nearly one-half of infants born to mothers infected with HIV presented with HIVDR to one or more non-nucleoside reverse transcriptase inhibitors (NNRTIs), one of the key classes of medicines for treatment and prevention of HIV transmission.[6 7] Minimising the spread of HIVDR is critical to ensure long-term efficacy and durability of ARV.

The global ARV drugs market value exceeded US$ 24.7 billion in 2018.[8] Projections suggest that it will be US$ 22.5 billion by 2024.

Substandard (due to within factory or supply chain errors) and falsified (due to fraud) (substandard and falsified, SF) medical products of all therapeutic classes have been found in many countries.[9 10] The WHO estimated that around 10.5% of medical products are SF in L/MIC, with an estimated US%30.5 billion financial loss.[11] A variety of defects have been found in SF medicines. They may contain one or several unexpected toxic active ingredients, too low or too high amounts of the expected active ingredients, they may contain none of the expected active ingredient(s) and they may also fail to dissolve properly, hence preventing the active ingredient(s) from reaching the blood stream, thus losing their efficacy. Hence, SF represent a serious public health problem. They also have a significant impact on clinical practice and the economy, and they generate loss of confidence in healthcare professionals and healthcare systems.[11] Antibiotics and antimalarials are the most studied classes of medicines.[12–15] A recent systematic review of the scientific literature showed that 17.4% of the 13 555 antibiotics tested for quality failed at least one quality test.[13] In another systematic review, 15.4% of the 3414 medicines used for cardiovascular diseases failed at least one quality test.[15] In both reviews, samples were mainly collected from low-income and middle-income countries and the number of samples tested per country was relatively small compared with the amount of medicines used globally. There is little scientific evidence publicly available on the quality of medicines available in high-income countries but the number and types of recalls by regulatory authorities show that these countries are not immune.[16–20]

Good quality ARVs are vital in the management of HIV infection and AIDS. The high number of people affected, the cost, the length of treatment and impaired access raise the risk of ARV falsification. Cases of SF ARV have been identified over the past decades and ARV are often quoted as medicines with common/recurring quality issues.[21–24] However, as far as, we are aware there is no clear understanding on the epidemiology of SF ARV globally. This systematic review was conducted with the key objective to summarise the available evidence on ARV medicines quality globally, to discuss their potential impact for patients and society.

## METHODS

### Search strategy

Search terms relevant to pharmaceutical quality (eg, 'falsified', 'substandard') were combined with search terms relevant to ARV and HIV/AIDS (online supplemental file 1). Systematic searches were conducted in Embase, PubMed, Google, Google Scholar and Web of Science in English and French up to 30 November 2021. The search terms were adapted for searches in MRA websites, and other websites with interest in medicines quality in English and French (online supplemental file 2). The articles from the first 20 pages of Google search results were screened for eligibility. Titles and abstracts were first screened and full texts of the identified articles were then assessed for eligibility. A manual search of the reference lists of the included articles was performed. Articles identified in previous systematic reviews by our group that included ARV medicines but not captured in our searches were also included.

### Eligibility criteria

Scientific articles and grey literature in English or French assessing or discussing the quality of ARV medicines were included. Articles containing scientific data on the prevalence of ARV medicines quality were the most relevant publications for this review. Other scientific articles included studies describing new tests or validation of innovative techniques to determine the quality of medicines in which ARV medicine samples were used to validate the technique, equivalence studies and quality control analyses. We also included reports of seizures, recalls, alerts by the MRAs or pharmaceutical companies and patients describing adverse reactions where the quality of the medicine was suspected to be the cause. The different types of study included in this review are described in online supplemental file 3.

We excluded data from publications describing the development/validation of analysis technique(s) for quality assessment of ARV medicines without sufficient information on the samples used and publications on the quality of herbal/mineral/animal part remedies claimed to treat HIV/AIDS.

We included medical devices for the diagnosis of HIV.

### Key definitions

Following the 2017 WHO definitions, falsified medicines are those that 'deliberately/fraudulently misrepresent their identity, composition or source'.[25] Substandard medicines are 'authorised medical products that fail to meet either their quality standards or their specifications, or both'.[25] This may result from negligence/errors during the manufacturing process or degradation through deterioration because of inappropriate storage/transport in the supply chain. There is inadequate evidence to distinguish poor quality medicines resulting from errors during

the manufacturing process from subsequent degradation in the supply chain due to heat and humidity.

Pharmaceutical analysis relies on compendial tests described in pharmacopoeial monographs. For finished medicines, monographs commonly include the identification and quantification of Active Pharmaceutical Ingredient (API) content (using sophisticated standardised techniques such as liquid chromatography coupled with various detectors), dissolution testing, detection of specific levels of predetermined impurities/related substances, uniformity of dosage units and additional attributes depending on the formulation of the product (eg, tablet friability). In many studies included in this review, not all pharmacopoeial analyses were conducted and also a variety of non-pharmacopoeial assays were used, for example, for investigating specific contaminants or unstated APIs. Assay details were not always provided making it difficult to standardise the definition of a 'failed sample'. Consequently, we define a failed sample as one for which at least one quality analysis test performed by the investigators gave a fail result, irrespective of the number and type of assays used.

As it is not possible to reliably classify a medicine as substandard or falsified without packaging analysis, products without packaging authentication that failed at least one quality test (ie, the results are outside the acceptable limits of the chosen specifications reference, either pharmacopoeia monograph or in-house specifications) are defined as 'substandard or falsified' (SorF).[14] However, all samples that contained incorrect or no API were assumed to be falsified, although there is a (limited) risk of misclassification of such samples as falsified when they are substandard, due to gross manufacturing errors.

As in previous systematic reviews by our group,[13 15 26] we define 'failure frequency' (FF) as the proportion of samples included in a prevalence survey that failed at least one quality test described in the report. We define a 'data point' as a specific location where medicines were collected for quality analysis, at a given time and for a given study. For medicines purchased online the location where the samples were received was extracted.

### Data collection

Data were manually extracted into the 'Online Medicine Quality Data Manager', an online data entry tool developed by the Infectious Diseases Data Observatory (IDDO) Informatics and the Lao-Oxford-Mahosot-Wellcome Trust Research Unit Medicine Quality team. Publication type (eg, report, original research article), year of publication, sampling type, location (country and city, where available) and type of outlet where samples were collected, the total number of samples collected, API/API combination name, number of samples failing medicine quality test(s), quality defect and the techniques that were used to analyse samples were entered in the online tool.

### Data analysis

FlySpeed SQL Query (V.3.5.4.2) was used to extract data from the online database and Microsoft Excel 2013 was used for data analysis. Qualitative variables were expressed as numbers and percentages (n (%)). Quantitative variables were expressed as median with first and third quartiles (Q1 and Q3, respectively).

### Quality of studies assessment: Medicine Quality Assessment Reporting Guidelines

The methodology and reporting of prevalence surveys were evaluated using the Medicine Quality Assessment Reporting Guidelines (MEDQUARG). MEDQUARG is a checklist of 26 items that should be included in reports of medicine quality surveys.[27] All criteria had to be fulfilled for each item to be awarded one point. Prevalence surveys were assessed independently by two reviewers with a third person resolving any disagreement. Only the prevalence surveys published as original articles in scientific journals, following the Introduction/Methods/Results/Discussion section or similar style and published as reports or PhD thesis, were assessed.

This review was registered in the International Prospective Register for Systematic Review (PROSPERO, Registration No: CRD42016039531) and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (online supplemental file 4).

### Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

## RESULTS

### Overall literature on ARV medicines quality

After duplicates removal, 21 462 out of 25 880 publications gathered through electronic searches were screened by title and abstract (figure 1).

In total, 216 publications were included in this review, of which more than half were original research articles (57.9% (n=125)) and 13.9% (n=30) were lay press (figure 2). Most original research articles (89.6%, 112/125) were published in peer-reviewed journals. The number of publications related to ARV medicines quality per year was low between 1990 and 2003, reached a peak in 2016 (n=28 publications) and then decreased (figure 2).

Of the 216 publications, 205 were on ARV medicines quality and eleven on the quality of medical devices used in HIV. Of the 205 publications on ARV quality, 76 (37.1%) described the quality of ARV medicines in a specific location at a specific time with a total of 455 data points, and 129 (62.9%) did not contain data point information. No publication on medical devices for HIV diagnosis contained data on their quality in a specific location at a specific time. Out of 76 publications with data points, 19 (25.0%) were prevalence studies, 15 (19.7%)

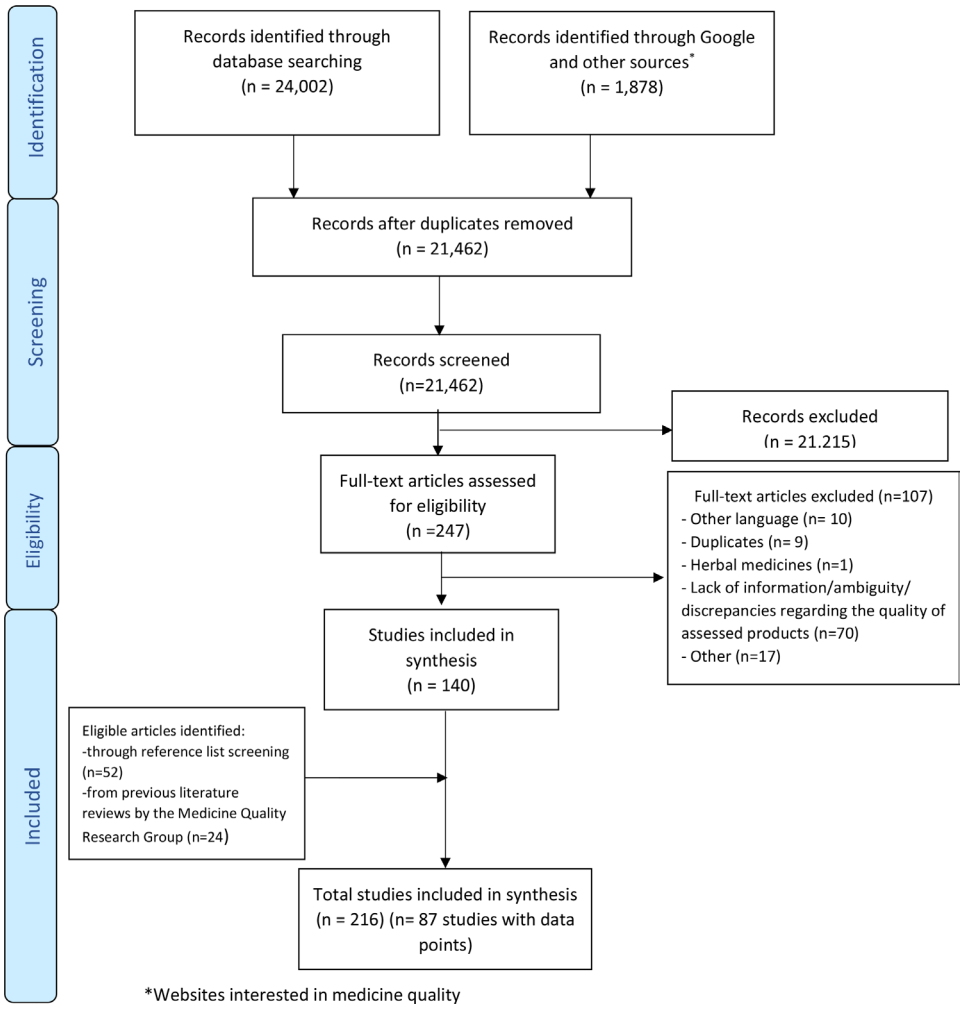


**Figure 1** PRISMA flow chart of the selection process of the publications on antiretroviral medicines quality. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

analytical technique development/validation, 8 (10.5%) routine quality control analysis, 4 (5.3%) equivalence studies, 1 (1.3%) bioavailability study and the data from the United States Pharmacopoeia's (USP) Medicines Quality Database were also included as one publication (1.3%) (online supplemental file 5). Others were recall/warning/alerts (n=16), seizures (n=7) and case reports (n=5) published in newspapers or medicines regulatory authorities websites.

A total of 4898 samples were collected and tested for quality, mainly in prevalence surveys (n=3713, 75.8%) and routine MRA quality control analysis (n=766, 15.6%). Of all samples, 59 (1.2%) failed at least one quality test. Of the failing samples, 54 (91.5%) were classified as SorF because no packaging analysis to assess the authenticity of the samples had been performed, 5 (8.5%) were substandard and no samples were classified as falsified.

All data are mapped and can be downloaded on the IDDO Medicine Quality Surveyor system (https://www.iddo.org/mqsurveyor/#antiretrovirals).

### Prevalence surveys

Nineteen prevalence surveys published between 2003 and 2021 were included. Overall 3713 samples of 22 different APIs or combinations of APIs were collected in 21 countries (168 data points) on 4 continents. The sample size per study ranged from 3 to 2630 samples with a median (Q1–Q3) of 16.0 (10.5–44.5) samples per prevalence survey. The overall FF in prevalence surveys was 1.4% (51/3,713). Of the failing samples, 47 (92.2%) were classified as SorF, 4 (7.8%) were substandard and no samples were classified as falsified.

Three prevalence surveys used random sampling to select the outlets to be included (FF 2.1%, 9/419), 14 used convenience sampling only (FF 1.2%, 38/3,247), 1 used mixed random and convenience sampling designs (FF 0.0%, 0/42), and the sampling strategy was not described in one survey (FF 80.0%, 4/5) (online supplemental file 6).

We found no publicly available evidence for 174/195 (89.2%) of national states. About three-fourths (75.8%, n=2813/3713) of samples in prevalence surveys were collected from low-income countries, 18.7% (n=695/3,713) and 0.1% (n=37/3,713) were collected in middle-income and high-income countries, respectively (table 1). One hundred and sixty-eight samples (4.5%) were part of a large multicountry study but the FF were

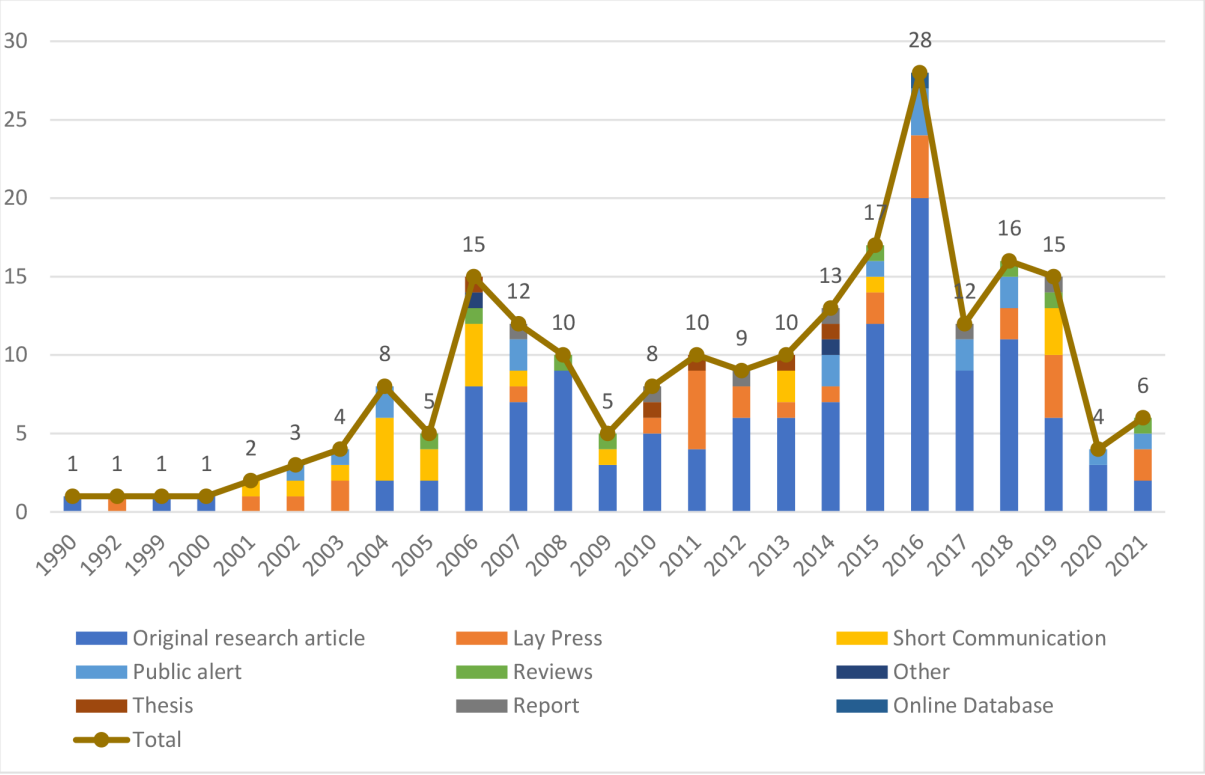


**Figure 2** Number of publications per type and year of publication. (Note: publications published up to the 30 November 2021 only were included).

not broken down by country. Over 90% (3675/3713) of samples included in prevalence surveys were procured in Africa and Asia, representing 97.0% (3603/3713) and 1.9% (72/3713) of all the samples, respectively.

The FF was the highest in the Americas (11.8%, 2/17), followed by Europe (9.5%, 2/21), but the total number of samples tested was low. The FF was 1.2% (45/3603) in Africa and 2.8% (2/72) in Asia. The highest number of samples was collected in Tanzania (n=2707), with an FF of 0.9% (24/2707).

The proportion of samples of Efavirenz collected in prevalence surveys was the highest (5.2%, 193/3713) with FF=3.6% (7/193), followed by nevirapine (5.2%, 192/3713) with FF=2.6% (5/192) and lamivudine-nevirapine-stavudine combination (3.8%, 177/3713) with FF=2.8% (5/177), respectively (table 2).

The FF of samples of ritonavir was the highest (100.0%, 2/2), followed by that of indinavir (42.9%, 6/14) but only few samples were tested.

Most of samples collected in prevalence surveys were tested for more than one quality attributes (93.8%, 3483/3713). Fourteen samples (1.4%, 14/1034) failed the API content test and 8 samples (1.3%, 8/616) failed the dissolution test. No sample (0.0%, 0/495) failed impurity/contaminant/related substances tests (online supplemental file 7).

Six samples out of 3256 (0.2 %) failed visual inspection of sample units (shape/colour uniformity, presence of contamination etc) and/or non-comparative packaging analysis (check of the availability of specific information and in some cases the conformity to packaging and labelling requirements with reference to MRA guidelines) in prevalence surveys. Of 14 samples that failed API content tests, 50.0% (7/14) contained lower API amount than stated, 42.9% (6/14) higher API amount and for 1 sample (7.1 %, 1/14) there was not enough information in the publication to determine whether it contained higher or lower amounts of API. Twelve out of 19 studies used High-Performance Liquid Chromatography (HPLC) methods (coupled with various detectors) for analysing API content (79.6%, 823/1034 samples).

The USP was the most commonly used (in 13/19 studies), followed by the British Pharmacopoeia and the International Pharmacopoeia (in 5 and 4 studies, respectively) (online supplemental file 6).

The highest FF was observed in samples collected from private pharmacies (28.0%, 7/25), followed by hospital/health centres (19.0%, 8/98), websites (7.7%, 2/26) and other government outlets (6.3%, 1/16) (online supplemental file 8). In total, 1302 samples were collected in multiple types of facilities with an FF of 2.2% (29/1302) but results of the quality tests were not given by outlet type. In additional, 2200 samples included in one study were collected in Tanzanian ports of entry with FF 0.0% (0/2200). For 21 samples, there was no information on the health facility where the samples were collected.

For the majority of the samples (93.3% (3464/3713)) included in prevalence surveys, there were no details on the stated manufacturer, or no breakdown of the samples by country of origin of the manufacturer (online

**Table 1** Failure frequency by continent/country in prevalence surveys

| Continent | Income | Country | No of publications | No of data points | Failure frequency % (n/N) |
|---|---|---|---|---|---|
| Americas | | | | | 11.8 (2/17) |
| | HIC | USA | 1 | 6 | 12.5 (2/16) |
| | UMIC | Jamaica | 1 | 1 | 0.0 (0/1) |
| Europe | | | | | 9.5 (2/21) |
| | HIC | Lithuania | 2 | 5 | 40.0 (2/5) |
| | HIC | UK | 1 | 3 | 0.0 (0/16) |
| Asia | | | | | 2.8 (2/72) |
| | UMIC | China | 1 | 3 | 33.3 (1/3) |
| | LMIC | Cambodia | 1 | 1 | 14.3 (1/7) |
| | LMIC | India | 1 | 7 | 0.0 (0/17) |
| | UMIC | Thailand | 1 | 3 | 0.0 (0/3) |
| | Unknown | Unknown* | 1 | 8 | 0.0 (0/42) |
| Africa | | | | | 1.2 (45/3603) |
| | LIC | Ethiopia | 1 | 4 | 25.0 (1/4) |
| | LMIC | Senegal | 2 | 9 | 14.5 (8/55) |
| | UMIC | South Africa | 3 | 9 | 9.1 (1/11) |
| | LMIC | Nigeria | 2 | 11 | 5.7 (4/70) |
| | LIC | DR Congo | 2 | 11 | 3.9 (2/51) |
| | LMIC | Zambia | 5 | 17 | 3.1 (2/65) |
| | LMIC | Cameroon | 2 | 11 | 1.4 (1/69) |
| | LIC | Tanzania | 3 | 23 | 0.9 (24/2707) |
| | Unknown | Unknown† | 1 | 1 | 0.8 (1/126) |
| | LMIC | Kenya | 3 | 26 | 0.3 (1/394) |
| | LIC | Uganda | 2 | 9 | 0.0 (0/51) |
| Total | | | 19 | 168 | 1.4 (51/3713) |

Because of the limited number of samples tested for quality in the studies included in this review, the figures should not be interpreted as representative of the prevalence of specific SF antiretroviral medicines (please refer to the discussion section of the current paper for more details).
*Multicountry study (Thailand and Vietnam) with no break down of the results by country.
†Multicountry study (Burkina Faso, Democratic Republic of the Congo, Nigeria, Rwanda and Zambia in Africa) with no break down of the results by country
DR Congo, Democratic Republic of the Congo; HIC, high-income country; LIC, low-income country; LMIC, lower-middle-income country; SF, substandard and falsified; UMIC, upper-middle-income country.

supplemental file 9). The FF of the samples stated as made by Asian manufacturers (6.4%, 238/3713), was of 3.8% (9/238). The FF of samples stated as made by American manufacturers was the highest (14.3%, 1/7).

The median (Q1%–Q3%) concordance with MEDQUARG items of 15 prevalence surveys that met the inclusion criteria for appraisal using MEDQUARG was 42.3% (34.6%–55.8%) (figure 3, online supplemental file 10).

### Quality of studies assessment

Although 10 surveys were reported after the publication of the MEDQUARG in 2009, none stated that the MEDQUARG guidelines were followed to report the findings. Three (20.0%) studies reported how the sample collectors presented to the seller (whether covert shopper, and what the sampler said/asked the seller) and 4 (26.7%) outlined the sampling design with sufficient details (online supplemental file 10). Only 40.0% (6/15) of the studies provided definitions on the quality of medicines or recognised the WHO definition. In 33.3% (5/15) of the surveys, the samples were clearly categorised as genuine, falsified or substandard or another equivalent terminology (or an explanation of the reason why this was not done); 33.3% (5/15) stated whether medicines were registered with the government in the location(s) sampled. Sixty per cent (10/15) of the studies reported with sufficient details the relationship between packaging and chemistry results. The MRA of the sampled country(ies) was either involved in the study (a representative of the MRA being an author in the paper) or was stated to be informed of its findings in four studies (26.7%).

### Seizures, recalls, case reports

Twenty-eight publications describing recalls/warning/alerts (n=16), seizures (n=7) and case reports (n=5) of SF ARV medicines were found during our searches (online supplemental file 11). Recalls of products of 14 APIs/combinations due to dissolution failure, API content or impurity/contaminant were found. In addition, 10 recalls/warning/alerts and seizures of HIV diagnostic test kit and HIV viral load for diagnostic test were identified

Table 2 Failure frequency by API/API combination in prevalence survey

| API/API combination | No of publications | No of data points | Failure frequency % (n/N) |
|---|---|---|---|
| Ritonavir | 1 | 2 | 100.0 (2/2) |
| Indinavir | 4 | 6 | 42.9 (6/14) |
| Lopinavir-ritonavir | 4 | 5 | 18.2 (8/44) |
| Lamivudine-zidovudine-nevirapine | 3 | 3 | 8.2 (7/85) |
| Stavudine | 6 | 13 | 4.2 (4/96) |
| Efavirenz | 10 | 23 | 3.6 (7/193) |
| Lamivudine-nevirapine-stavudine | 7 | 14 | 2.8 (5/177) |
| Nevirapine | 12 | 24 | 2.6 (5/192) |
| Zidovudine | 7 | 18 | 1.9 (2/103) |
| Lamivudine | 6 | 18 | 1.5 (2/132) |
| Lamivudine-zidovudine | 5 | 11 | 1.5 (2/134) |
| Antiretroviral-unspecified | 2 | 2 | 0.0 (1/2,325) |
| Abacavir | 3 | 3 | 0.0 (0/33) |
| Abacavir-lamivudine | 1 | 1 | 0.0 (0/1) |
| Amprenavir | 1 | 1 | 0.0 (0/1) |
| Didanosin | 4 | 4 | 0.0 (0/20) |
| Efavirenz-lamivudine-tenofovir disiproxil | 1 | 1 | 0.0 (0/29) |
| Emtricitabine-efavirenz-tenofovir disiproxil | 2 | 2 | 0.0 (0/28) |
| Emtricitabine-tenofovir disoproxil | 2 | 4 | 0.0 (0/30) |
| Lamivudine-stavudine | 4 | 5 | 0.0 (0/43) |
| Saquinavir | 1 | 2 | 0.0 (0/2) |
| Tenofovir disoproxil | 3 | 5 | 0.0 (0/25) |
| Tenofovir disoproxil-lamivudine | 1 | 1 | 0.0 (0/3) |
| Total | 19 | 168 | 1.4 (51/3713) |

Because of the limited number of samples tested for quality in the studies included in this review, the figures should not be interpreted as representative of the prevalence of specific SF antiretroviral medicines (please refer to the discussion section of the current paper for more details).
API, active pharmaceutical ingredient; SF, substandard and falsified.

(online supplemental file 12). Those include the substitution of 140 000 HIV rapid diagnostic test (RDT) kits by urinary pregnancy tests or resale of just-past expiry kits in India,[28] and recall of one million of HIV testing kits in Kenya out of concern that they give false negative results.[29]

Other publications included in our review are listed in online supplemental file 13.

## DISCUSSION

We synthesised the publicly available evidence on the quality of ARV medicines from different publicy accessible sources. Overall, 1.4% of 3713 ARV samples collected in 21 countries failed at least 1 quality test in the 19 prevalence studies. The limited sample sizes of the studies impede interpretation of the results. Drawing conclusions on the impact of SF ARV for patients and the community is also rendered difficult by the limited reporting of the findings in the various prevalence surveys, and often by the bias generated by their limited methodology, as described by others.[30 31]

The observed FF in this review is lower than the 4.2% (43/1,018) failure rate described in a recent review of the literature of studies conducted between 2007 and 2016 by the WHO.[11] One recent study may result in underestimating the FF.[32] In this study, from which more than half of the samples (2630 samples) described in the current review originated, 2200 samples collected at ports of entry in Tanzania over 4 years passed the Global Pharma Health Fund(GPHF)-Minilab initial screening tests, which included simple visual inspection of dosage units, API identification by thin-layer chromatography and disintegration tests. These 2200 samples were not further tested by reference testing in the laboratory. However, the same report describes that 10% samples of samples collected in other health structures that passed GPHF-Minilab screening were further tested using laboratory reference testing, resulting in an FF of 3%. Though the GPHF-Minilab has shown good performances to identify

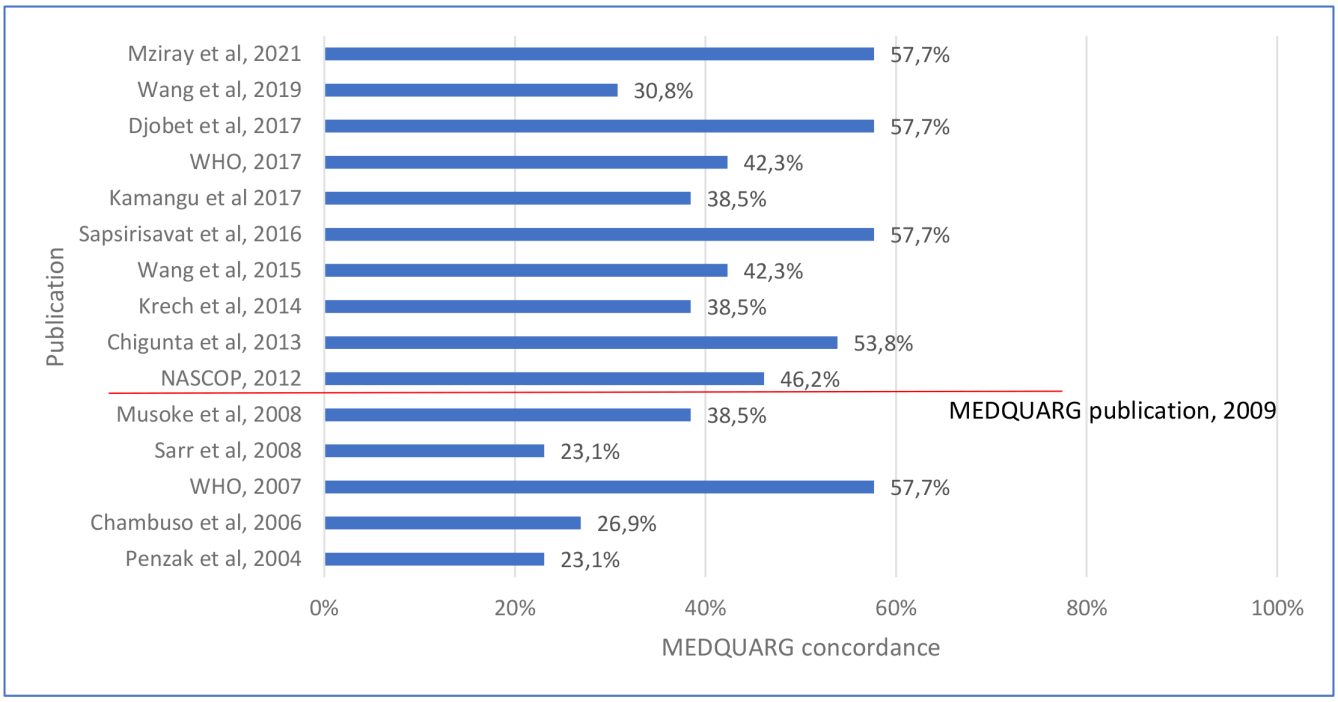


**Figure 3** Percentage of concordance of the 15 prevalence surveys with the 26 items included in MEDQUARG checklist. MEDQUARG, Medicine Quality Assessment Reporting Guidelines.

falsified samples containing none of the stated API, its sensitivity to identify substandard medicines containing lower or higher amounts of API is much lower.[33] If the same 3% FF was applied to the 2200 samples collected in ports, the FF in this review would have been more than double (3.1% (117/3713)).

SF 'HIV/hepatitis medicines' represented 43/1500 (2.9%) of rapid alerts of reports to the Global Surveillance and Monitoring System between 2013 and 2017.[9] Although ARVs are often quoted as one of the most affected products, together with other anti-infectives, the FF for ARV estimated here falls below that of other classes of medicines described in previous systematic reviews using the same methodology, such as for antibiotics (FF of 17.4% (2357/13 555)) and cardiovascular medicines (FF of 15.4% (525/3414)).[13 15] In those reviews, samples were frequently procured in private sector's facilities such as retail pharmacies, unlike in the current review in which an FF of 28.0% was observed in samples collected from private retail pharmacies, but only 25 samples were collected. ARV are often procured in LMIC within public or NGO vertical programmes which often follow stringent quality assurance systems and procure only WHO-prequalified medicines. However, in 2011 in Kenya nurses identified a falsified version of the ARV Zidolam-N, a WHO prequalified product, in Médecins Sans Frontières supplies relabelled fraudulently to extend its expiry date.[34]

The most common quality defects observed in prevalence surveys were lower or higher API content than stated on the label, failed dissolution tests (either too rapid or too slow), and impurity/contaminant/related substances tests. API in higher concentrations than expected risks not only poor outcomes to patients, but also lack of adherence through more frequent side effects. Using ARV medicines with too low API content and/or poor dissolution may lead to treatment failure, prolonged illness or death, and risks engendering the spread of drug resistant pathogens, although, as far as we are aware, the link between SF ARV and the emergence and spread of resistance has not been demonstrated.[35]

We found no publicly available evidence for almost 90% of national states, and for 17 of the 30 countries that bear 89% of the new HIV infections,[36] which indicates an important lack of oversight of the risks. We found no study on the quality of dolutegravir, though this might be due to its only recent recommendation for use by the WHO (in combination with two NNRTIs) for newly diagnosed HIV patients.[37] We also found limited information on tenofovir-based oral combinations recommended in 2015 by the WHO for pre-exposure prophylaxis (PrEP).[38] An increasing number of countries are including self-testing of HIV in their national policies. Cases of SF RDTs show the importance of postmarket surveillance of diagnostic kits. However, no studies trying to better understand the extent of quality issues of RDTs were identified.

Due to convenience, increasing accessibility to, perceived economical and confidential advantages of the internet, especially in the context of HIV/AIDS associated stigma and discriminations, online purchase of ARV is likely to increase. This may be particularly relevant to people searching for oral PrEP when at high risk of infection. In 2020, 130 countries had adopted the WHO recommendations on oral PrEP in national guidelines.[39] Only two prevalence studies described the quality of ARV

purchased on the internet, with too few samples collected to comment on the results.[40 41]

### Limitations

Searches were conducted only in English and French, risking the exclusion of articles, for example in Latin America, and we identified recalls/seizures/case reports mainly from searches in a limited number of MRA's websites and other websites interested in medicine quality. Unpublished postmarketing surveillance results from other MRAs and the pharmaceutical industry were not captured. Most studies were of small sample size and used convenient sampling which risk bias. The quality of reporting of prevalence surveys was poor as reflected by the low MEDQUARG scores. The quality of samples was assessed by different pharmacopoeia references. In most prevalence surveys, we found limited information on stated country of manufacture and more than one-third of the samples were collected in one study in different outlets but no details on the quality of the samples by type of outlet were given. We, thus, did not perform further analysis that could lead to misleading interpretation.

The diversity of and the often poor methodology and reporting of the studies renders the findings of systematic reviews of medicine quality difficult to interpret and extrapolate,[30 31] though we believe it is the best method to summarise the current evidence on the quality of different classes of medicines.

### Recommendations

There are clear gaps in the understanding of the epidemiology of SF ARV and related diagnostic tests. Initiatives such as the Distributed Pharmaceutical Analysis Laboratory (DPAL), a collaboration established between 30 academic institutions around the world to determine the quality of medicines collected from partner organisations in L/MICs, may facilitate better understanding of the epidemiology of SF medicines and other medical products.[42] Although packaging analysis is difficult, especially in obtaining voucher samples, it is vital to allow the objective distinction between substandard and falsified products. That 92.2% of failing samples were classified as SorF is a major impediment for deciding on policy as interventions to counter substandard and falsified differ.

Key current global public health aims are the 95-95-95 target of the Sustainable Development Goals by 2026 and to end AIDS by 2030.[36 43] Diagnosing 95% and achieving viral suppression in 95% of all HIV-positive individuals risks failure even if only 1% of the ARV/RDT available on the market do not fulfil their roles because they are poor quality. With millions of people being treated or using ARV for the prevention of HIV, even a small proportion of poor quality ARV with impaired efficacy or increased toxicity will greatly endanger the lives of millions, not only those treated, but also those who may be infected as a result of transmission from people using SF ARV. A related issue is concern about the quality of condoms, with many incidents and seizures of tons of falsified condoms with holes,[44–47] but the extent of the problem is also unknown. Gaps in the scientific evidence impede development of objective action plans on how best to secure the supply chains for ARV, RDT and other medical devices such as condoms. With the current goals set by international actors to scale up community based approaches for both treatment and prevention, such as community drug distribution, safeguards to ensure quality ARV and RDT will be crucial. More efforts also need to be put into controlling the quality of medicines available on the internet.

Shortages of good quality ARV create opportunities for substandard and falsified ARV medicines to reach supply chains. Shortages are exacerbated during the COVID-19 pandemic, as land, sea and air transport services shut down. People had difficulties to access ARV because of travel restrictions, disruptions in health services within countries and worsening of the economic situation because of the pandemic.[48] Better preparedness is needed for the next pandemic, for medical products to treat the pandemic's causing agent and for other medical products vital to millions such as ARV.

In view of the limitations described above, prevalence surveys with robust survey methodology adequate sample sizes, and better reporting of findings, in wider geographical regions including HIC and online sales are needed for a more comprehensive epidemiological information on the quality of ARV medicines. This would allow examination of trends over time and the impact of SF ARV on humans and their economy.

## CONCLUSION

Even a small proportion of SF ARV is unacceptable, as it may result in a myriad of HIV positive people not receiving the correct treatment, risking poor outcomes and resistance, and those using ARV as prophylaxis unknowingly being unprotected against infection. These results cannot represent an exact prevalence of poor quality ARV drugs globally but are a warning sign. The methodological limitations do not allow exptrapolation that 1.4% of ARV globally are SF. There is clearly a risk and more data on the epidemiology of SF ARV, facilitation of packaging analysis and optimisation of devices for their screening of SF products in supply chains are needed.

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**Contributors** CC, PN, PB and NTD designed the review. PB and NTD conducted the literature assessment. Screening and extraction were performed by PB and NTD under the supervision of CC. PB, NTD and CC assessed the quality of reporting of the surveys. NTD performed the analysis under the guidance of PN and CC.

NTD and CC prepared the first manuscript draft. CC, PN and PB provided revisions and CC and PN also provided guidance on the overall direction of the study. All authors approved the final version for publication. CC as the guarantor, accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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**Supplementary file 1: Search terms used for each source in the systematic review of the quality of ARV medicines**

| Sources | English search Terms |
|---|---|
| Pubmed | (“quality control” OR “drug quality” OR “quality analysis” OR counterfeit OR fake OR falsified OR spurious OR substandard OR “medicine quality” OR “pharmaceutical quality”) AND (antiretroviral OR anti-retroviral OR ARV OR HIV OR “Human Immunodeficiency Virus” OR AIDS OR “Acquired Immune Deficiency Syndrome”) |
| Embase | ('quality control' OR 'drug quality' OR 'quality analysis' OR counterfeit OR fake OR falsified OR spurious OR substandard OR 'medicine quality' OR 'pharmaceutical quality') AND (antiretroviral OR anti-retroviral OR ARV OR HIV OR 'Human Immunodeficiency Virus' OR AIDS OR 'Acquired Immune Deficiency Syndrome') |
| Web of Science | ('quality control' OR 'drug quality' OR 'quality analysis' OR counterfeit OR fake OR falsified OR spurious OR substandard OR 'medicine quality' OR 'pharmaceutical quality') AND (antiretroviral OR anti-retroviral OR ARV OR HIV OR 'Human Immunodeficiency Virus' OR AIDS OR 'Acquired Immune Deficiency Syndrome') |
| Google Scholar | (substandard OR “medicine quality” OR “pharmaceutical quality”) AND (anti-retroviral OR AIDS) |
| | (“quality control” OR “drug quality ” OR “quality analysis”) AND (“Human Immunodeficiency Virus”) |
| | (counterfeit OR fake OR falsified OR spurious) AND (antiretroviral OR anti-retroviral OR ARV OR HIV) |
| | (substandard OR “medicine quality” OR “pharmaceutical quality”) AND (“Human Immunodeficiency Virus”) |
| | (“quality control” OR “drug quality” OR “quality analysis”) AND (antiretroviral OR anti-retroviral) |
| | (“quality control” OR “drug quality” OR “quality analysis”) AND (ARV OR HIV OR AIDS) |
| | (counterfeit OR fake OR falsified OR spurious) AND (“Human Immunodeficiency Virus” OR AIDS) |
| | (counterfeit OR fake OR falsified OR spurious) AND (“Acquired Immune Deficiency Syndrome”) |
| | (substandard OR “medicine quality” OR “pharmaceutical quality”) AND (antiretroviral OR ARV OR HIV) |
| | (“pharmaceutical quality”) AND (“Acquired Immune Deficiency Syndrome”) |
| | (substandard OR “medicine quality”) AND (“Acquired Immune Deficiency Syndrome”) |
| Google | (“quality control” OR “drug quality” OR “quality analysis” OR counterfeit OR fake OR falsified OR spurious OR substandard OR “medicine quality” OR “pharmaceutical quality”) AND (antiretroviral OR anti-retroviral OR ARV OR HIV OR “Human Immunodeficiency Virus” OR AIDS OR “Acquired Immune Deficiency Syndrome”) |
| **Sources** | **French search Terms** |
| | (“contrôle qualité” OR "qualité des médicaments" OR “analyse de qualité”) AND (antirétroviral) |
| | (sous-standard OR “ qualité de médicament” OR “qualité pharmaceutique”) AND (antirétroviral) |
| | ("faussement étiqueté" OR contrefait) AND (“syndrome d'immunodéficience acquise”) |
| | ("faussement étiqueté" OR contrefait) AND ("virus de l'immunodéficience humaine") |

| | |
|---|---|
| Google Scholar | (“contrôle qualité” OR "qualité des médicaments" OR “analyse de qualité”) AND (antirétroviral) |
| | (“contrôle qualité” OR "qualité des médicaments") AND (“syndrome d'immunodéficience humaine) |
| | (sous-standard) AND ("virus de l'immunodéficience humaine" OR “syndrome d'immunodéficience acquise") |
| | (contrefaçon OR "faux médicament" OR "médicament fallacieux" OR falsifié) AND (ARV OR VIH OR SIDA) |
| | (sous-standard OR “ qualité de médicament” OR “qualité pharmaceutique”) AND (antirétroviral) |
| | (“qualité de médicament” OR “qualité pharmaceutique”) AND ("virus de l'immunodéficience humaine) |
| | ("faux médicament" OR "médicament fallacieux") AND (“syndrome d'immunodéficience acquise”) |
| | (“contrôle qualité” OR "qualité des médicaments") AND ("virus de l'immunodéficience humaine") |
| | ("faussement étiqueté" OR contrefait) AND (antirétroviral) |
| | (“qualité de médicament” OR “qualité pharmaceutique”) AND (“syndrome d'immunodéficience acquise”) |
| | (“analyse de qualité” OR contrefaçon OR falsifié) AND ("virus de l'immunodéficience humaine") |
| | ("faux médicament" OR "médicament fallacieux") AND ("virus de l'immunodéficience humaine) |
| | ("faussement étiqueté" OR contrefait) AND (ARV OR VIH OR SIDA) |
| | (“analyse de qualité” OR contrefaçon OR falsifié) AND (“syndrome d'immunodéficience acquise”) |
| | (“contrôle qualité” OR "qualité des médicaments" OR “analyse de qualité”) AND (ARV OR VIH OR SIDA) |
| | (contrefaçon OR "faux médicament" OR "médicament fallacieux" OR falsifié) AND (antirétroviral) |
| | (sous-standard OR “qualité de médicament” OR “qualité pharmaceutique”) AND (ARV OR VIH OR SIDA) |
| Google | (“contrôle qualité” OR "qualité des médicaments" OR “analyse de qualité” OR contrefaçon OR "faux médicament" OR "médicament fallacieux" OR falsifié OR sous-standard OR “qualité de médicament” OR “qualité pharmaceutique” OR "faussement étiqueté" OR contrefait) AND (antirétroviral OR antirétroviral OR ARV OR VIH) |
| | (“contrôle qualité” OR "qualité des médicaments" OR “analyse de qualité” OR contrefaçon OR "faux médicament" OR "médicament fallacieux" OR falsifié OR sous-standard OR “qualité de médicament” OR “qualité pharmaceutique” OR "faussement étiqueté" OR contrefait) AND ("virus de l'immunodéficience humaine" OR SIDA) |
| PubMed | (“contrôle qualité” OR "qualité des médicaments" OR “analyse de qualité” OR contrefaçon OR "faux médicament" OR "médicament fallacieux" OR falsifié OR sous-standard OR “qualité de médicament” OR “qualité pharmaceutique” OR "faussement étiqueté" OR contrefait) AND (antirétroviral OR antirétroviral OR ARV OR VIH OR "virus de l'immunodéficience humaine" OR “syndrome d'immunodéficience acquise ”OR SIDA) |
| Embase | (“contrôle qualité” OR "qualité des médicaments" OR “analyse de qualité” OR contrefaçon OR "faux médicament" OR "médicament fallacieux" OR falsifié OR sous-standard OR “qualité de médicament” OR “qualité pharmaceutique” OR "faussement étiqueté" OR contrefait) AND |

| | |
|---|---|
| | (antirétroviral OR antirétroviral OR ARV OR VIH OR "virus de l'immunodéficience humaine" OR “syndrome d'immunodéficience acquise ”OR SIDA) |
| Web of Science | (“contrôle qualité” OR "qualité des médicaments" OR “analyse de qualité” OR contrefaçon OR "faux médicament" OR "médicament fallacieux" OR falsifié OR sous-standard OR “qualité de médicament” OR “qualité pharmaceutique” OR "faussement étiqueté" OR contrefait) AND (antirétroviral OR antirétroviral OR ARV OR VIH OR "virus de l'immunodéficience humaine" OR “syndrome d'immunodéficience acquise ”OR SIDA) |

**Supplementary file 2. Websites used for information gathering about substandard and falsified antiretroviral medicines**

| | Websites names and hyperlinks | | Websites names and hyperlinks |
|---|---|---|---|
| **International Organisations and NGOs** | ++ Health Action International ++ | **Medicine Regulatory Authorities and national bodies** | Centers for Disease Control and Prevention |
| | ACG - Anti-counterfeting group | | Comité national anti-contrefaçon |
| | Coalition Against Illicit Trade | | Fraud.org |
| | EAASM-European Alliance for Access to Safe Medicines | | NAFDAC Nigeria |
| | Fondation Chirac - Agir au service de la paix | | Ghana FDA |
| | GACG Global Anti-Counterfeiting Network | | HSA Health Sciences Authority Singapore |
| | GPHF The Global Pharma Health Fund | | Medicines and Healthcare products Regulatory Agency, UK Government |
| | IACC-International AntiCounterfeiting Coalition | | US Food and Drug Administration |
| | Medical Products Counterfeiting and Pharmaceutical Crime ( INTERPOL) | | Kenya Pharmacy and poisons Board |
| | IRACM Institut de Recherche Anti-Contrefaçon de Médicaments | | Central Drugs Standard Control Organization |
| | L'Office des Nations unies contre la drogue et le crime | | Ordre national des pharmaciens de côte d'ivoire |
| | MIMS | | |
| | MSF Access Campaign msfaccess.org | **Alert lists and systems** | Campaign for Safe Medicines in Kenya |
| | Permanent Forum on International Pharmaceutical Crime | | Minilabs save lives |
| | PhaReD Foundation - Home | | mPedigree Network Bringing Quality To Life<br>Innovative Global Partnerships Against Fake Drugs |
| | Pharmelp Detection of counterfeit medicines | | Pharmabiz |
| | ReMeD-Réseau Médicaments & Développement | | PharmaSecure |
| | Safe Medicines India | | Sproxil Protecting Brands Globally |
| | Safemedicines Protecting the Safety of America's Drug Supply | | Association Développement et Santé |
| | The Medicrime Convention | | ContrefaçonRiposte |
| | Third World Network (TWN) | | |
| | USP Promoting the Quality of Medicines (PQM) | | |
| **Academic/ Research Initiatives** | QUAMED - Quality Medicines for All | **Newspaper websites with interest in** | allafrica.com |
| | IRASEC- Institut de Recherche sur l'Asie du Sud-Est Contemporaine | | Daily Monitor - Uganda News, Politics, Business, Travel, Health, Sports, News Paper, technology |
| | | | Ghanaweb |
| | | | L'ESSOR journal Mali |

| | | | |
|---|---|---|---|
| **Pharmaceutical Industry** | Sanofi | **medicine quality** | ModernGhana |
| | Les entreprises du médicament | | Nigerian Tribune |
| | Pfizer Pharmaceutical News and Media Pfizer One of the world's premier biopharmaceutical companies | | Rapideinfo-Journal Mauritanie |
| | PSI-Inc.org | | THE HANS INDIA |

**Supplementary file 3: Types of studies included in the review and definition**

| | Study/report type | Definition |
|---|---|---|
| **Scientific reports** | Quality control | Study in which samples were collected to be analyzed in routine post-marketing surveillance by MRAs or a laboratory mandated by MRAs |
| | Prevalence survey | Study in which samples were collected within the pharmaceutical supply chain to assess their quality, to describe the prevalence of circulating SF medicines |
| | Equivalence study | Study to assess the quality of different marketed brands of the same API(s) assuming that the results of the collected samples would represent the quality of the brand as a whole and not an estimate of the frequency of individual samples of different quality |
| | Analysis technique development/validation | Study in which samples are assembled in a laboratory to answer a chemical, rather than an epidemiological question (mostly for the development of a new quality technique) |
| | Bioavailability study | Study of the in vivo bioavailability, i.e. testing for adequate body tissue concentration including the rate and extent to which drug reaches the body tissue compartment |
| **Other reports** | Recall/warning/alert | Recall/Warning/Alert of products by manufacturers via MRA or by MRAs directly, or by WHO rapid alert |
| | Case reports | Patients not responding to medicines or adverse drug reactions where the quality of the medicine was suspected as the cause. Also includes samples analyzed for quality not included in a scientific study. |
| | Seizure | Confiscations by police or MRA |

**API, Active Pharmaceutical Ingredient; MRA, Medicines Regulatory Agency; WHO, World Health Organization**

## Supplemental material 4-PRISMA checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2-3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 5-6 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 6 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 10 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 6-8 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 6 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 6 & Supplemental 1 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 6-8 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 9 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 9 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 10 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 9 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 9 |

## Supplemental material 4-PRISMA checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 10 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | N/A |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 10-11, Figure 1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Supplemental 6 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 21 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Supplemental 6, 12, 14 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 10-16 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 16 & Supplemental 10 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | No additional |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 17-18 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 17; 19-20 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 17-21 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 22 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

**Supplementary file 5** : Number of publications, data points and samples per study/report type in publications (either scientific studies or other reports) containing description of the quality of antiretroviral medicines/medical devices in data point(s), i.e. in a specific location at a specific time

| | Study type | No. publications n (%) | No. data points n (%) | No. samples n (%) |
|---|---|---|---|---|
| **Scientific reports** | Prevalence survey | 19 (25.0%) | 168 (36.8%) | 3713 (75.8%) |
| | Quality control | 8 (10.5%) | 46 (10.1%) | 766 (15.6%) |
| | Analytical technique development/validation | 15 (19.7%) | 20 (4.4%) | 35 (0.7%) |
| | Equivalence study | 4 (5.3%) | 5 (1.1%) | 18 (0.4%) |
| | Bioavailability studies | 1 (1.3%) | 2 (0.4%) | 0 (0.0%) |
| | Unknown* | 1 (1.3%) | 177 (38.8%) | 366 (7.5%) |
| | **Total** | **48 (63.2%)** | **418 (91.7%)** | **4,898 (100%)** |
| **Other reports** | Recall/warning/alert | 16 (21.1%) | 21 (4.6%) | |
| | Seizure | 7 (9.2%) | 10 (2.2%) | |
| | Case reports | 5 (6.6%) | 7 (1.5%) | |
| | **Total** | **28 (36.8%)** | **36 (8.3%)** | |
| **Total** | | **76 (100.0%)** | **456 (100.0%)** | |

*Data from the Medicines Quality Database (MQDB) of United States Pharmacopeia

## Supplementary file 6: Main Characteristics of prevalence surveys of antiretroviral medicines

| Reference / country of collection | Active pharmaceutical ingredient (API) | Brand name | Outlet/ Sampling type | Reference specifications stassindard | Test (s) performed and main analytical technique | No. Failed n (%) |
|---|---|---|---|---|---|---|
| Penzak, S.R. 2003 [1] Kenya, Lithuania, Zambia, South Africa | Nevirapine | Triomune 40<br>Nevimune(200)<br>Nevirex<br>Viramune (Nev 200)<br>Triomune 30 | Private pharmacy/ Convenience | Unspecified | API content<br><br>*High-performance liquid chromatography /ultraviolet (HPLC-UV)* | 0 /6 (0.0%) |
| Ramachandran, G. 2004 [2] Zimbabwe, South Africa, Lithuania, Jamaica, Zambia | Efavirenz<br>Indinavir<br>Lopinavir-ritonavir<br>Amprenavir<br>Ritonavir<br>Saquinavir soft-gel capsules | Sustiva<br>Stocrin<br>Crixivan<br>Indivex-400<br>Kaletra<br>Agenerase<br>Norvir<br>Fortovase | Unspecified/ Convenience | United States Pharmacopeia (USP) /National Formulary | API content<br><br>*HPLC-UV* | 3/12 (25.0%) |
| Ramachandran, G, 2004 [3] India | Lamivudine-Nevirapine-Stavudine<br>Efavirenz<br>Nevirapine<br>Zidovudine<br>Stavudine<br>Lamivudine<br>Didanosin | Unspecified | Manufacturer/ Convenience | Unspecified | API content<br><br>*HPLC-UV* | 0/17 (0.0%) |
| Ciss, M. 2006 [4] Senegal | Stavudine<br>Nevirapine<br>Indinavir | Unspecified | Combination of outlets / Convenience | USP + European Pharmacopeia + International Pharmacopoeia | API content<br><br>*HPLC-unknown detector* | 1/12 (8.3%) |
| M.H.Chambuso, 2006 [5] Tanzania | Indinavir<br>Stavudine | Unspecified | Private pharmacy/ Unspecified | British Pharmacopoeia (BP) + USP | API content, API identification, Dissolution, Visual inspection<br><br>*UV-visible spectrophotometry* | 4/5 ( 80.0%) |
| WHO, 2007 [6] Uganda, Tanzania, | Didanosin, Efavirenz, Lamivudine, Nevirapine, Stavudine, Zidovudine, | Unspecified | Combination of outlets / Random | Brazilian Pharmacopeia, USP 2008 | API content, Content uniformity, Dissolution, weight, Visual inspection, impurity, API identification | 8/394 (2.0%) |

| Reference / country of collection | Active pharmaceutical ingredient (API) | Brand name | Outlet/ Sampling type | Reference specifications stassindard | Test (s) performed and main analytical technique | No. Failed n (%) |
|---|---|---|---|---|---|---|
| Democratic Republic of the Congo, Zambia, Kenya, Nigeria, Cameroon | Lamivudine-Zidovudine, Lamivudine-Nevirapine-Stavudine | | | | *HPLC-UV/Vis* | |
| Sarr, S. O. 2008 [7] Senegal | Didanosin<br>Indinavir<br>Lamivudine<br>Nevirapine<br>Stavudine<br>Zidovudine | Unspecified | Hospital/health centres / Convenience | Unspecified | API content (semi-quantitation), Disintegration, Visual inspection<br><br>*Thin Layer Chromatography (TLC)* | 7/43 (16.3%) |
| Musoke. D 2008 [8] Uganda | Lamivudine-Nevirapine-Stavudine | Unspecified | Hospital/health centres / Random | USP | API content, Visual inspection, dissolution<br><br>*HPLC-Ultra-Violet* | 0/14 (0.0%) |
| Munkombwe, D 2010 [9] Zambia | Nevirapine<br>Lamivudine-Nevirapine-Stavudine<br>Efavirenz<br>Lamivudine-Stavudine | Unspecified | Government outlets/ Random | BP + USP | API content, API identification<br><br>*TLC* | 1/11 (9.1%) |
| NASCOP 2012 [10] Kenya | Abacavir<br>Abacavir-Lamivudine<br>Didanosin<br>Efavirenz<br>Emtricitabine-Efavirenz-Tenofovir Disiproxil<br>Lamivudine<br>Lamivudine-Stavudine<br>Lamivudine-Nevirapine-Stavudine<br>Lamivudine-Zidovudine<br>Lamivudine-Zidovudine-Nevirapine<br>Nevirapine<br>Stavudine<br>Tenofovir Disoproxil<br>Tenofovir disoproxil – Lamivudine | Unspecified | Combination of outlets / Convenience | BP + USP | API content, Dissolution, weight, Friability<br><br>*HPLC- Unknown detector* | 1/284 (0.4%) |

| Reference / country of collection | Active pharmaceutical ingredient (API) | Brand name | Outlet/ Sampling type | Reference specifications stassindard | Test (s) performed and main analytical technique | No. Failed n (%) |
|---|---|---|---|---|---|---|
| | Zidovudine Lopinavir-Ritonavir | | | | | |
| Chigunta, M.[11] 2013 Zambia | Nevirapine | Unspecified | Combination of outlets/ Convenience | USP | API content , API identification, Visual inspection<br><br>*HPLC – unknown detector* | 0/9 (0.0%) |
| Krech. L.A. 2014 [12] Cambodia | Lamivudine-Nevirapine-Stavudine | Unspecified | Combination of outlets/ Convenience | USP and Cambodia Pharmacopeia | Visual inspection, API content , API identification, Impurity, Disintergration<br><br>*HPLC, TLC* | 1/7 (14.3%) |
| Wang, T. 2015 [13] Thailand, Nigeria, Ethiopia, China, United States of America, South Africa | Lamivudine Nevirapine Zidovudine Efavirenz | Unspecified | Government outlets, Non-governmental organization, Website, Private pharmacy / Convenience | USP | API content, Visual inspection, Impurity<br><br>*HPLC-UV* | 6/46 (13.0%) |
| Sapsirisavat, V. 2016 [14] Thailand, Viet Nam | Lopinavir-Ritonavir Tenofovir Efavirenz | | Combination of outlets / Random and convenience | WHO International Pharmacopoeia | API content, API identification, Uniform of mass, Dissolution<br><br>*Pharmacopeial techniques followed, no detail of the specific techniques* | 0/42 (0.0%) |
| Kamangu, E.N. 2017 [15] Democratic Republic of the Congo | Abacavir Zidovudine Efavirenz Nevirapine | Nevipan (200) Nevimune (200) Nevirapine (200) EstivaN Aviroz Abacavir sulfate | Hospital/health centres / Convenience | European Pharmacopoeia, BP, International Pharmacopoeia 6th Edition. | API content, Disintegration, Friability<br><br>*UV-visible spectrophotometry* | 1/10 (10.0%) |
| WHO 2017 [16] Burkina Faso, Democratic Republic of the | Unspecified | Unspecified | Combination of outlets / Convenience | BP+USP+ International Pharmacopoeia | Where applicable: Appearance, API identification, API content , Weight variation, Dissolution, Impurity, Related substances, Fineness of | 1/126 (0.8%) |

| Reference / country of collection | Active pharmaceutical ingredient (API) | Brand name | Outlet/ Sampling type | Reference specifications stassindard | Test (s) performed and main analytical technique | No. Failed n (%) |
|---|---|---|---|---|---|---|
| Congo (DRC), Nigeria, Rwanda and Zambia. | | | | | dispersion, Water content – no details on results per test<br><br>*TLC, HPLC -unknown detector, IR (depending on API and formulation)* | |
| Djobet. M.P.N 2017 [17] Cameroon | Efavirenz<br>Lamivudine-Stavudine<br>Nevirapine<br>Lamivudine-Zidovudine-Nevirapine<br>Lamivudine-Zidovudine | Unspecified | Combination of outlets / Convenience | USP | API content , API identification, Visual inspection, Disintegration<br><br>*UV Spectrophotometry*<br>*TLC* | 0/35 (0.0%) |
| Wang, X 2019 [18] United Kingdom | Emtricitabine-Tenofovir Disoproxil | Unspecified | Website , Hospital/health centers / Convenience | Unspecified | API content , API identification<br><br>*Ultra-Performance Liquid Chromatography (UPLC)* | 0/16 (0.0%) |
| Mziray S 2021 [19] Tanzania | Efavirenz<br>Nevirapine<br>Lamivudine<br>Zidovudine<br>Tenofovir Disoproxil Fumarate<br>Lamivudine/Zidovudine<br>Abacavir Sulphate<br>Lopinavir/Ritonavir<br>Tenofovir Disoproxil Fumarate /Emtricitabin<br>Tenofovir Disoproxil Fumarate /Lamivudine/ Efavirenz<br>Lamivudine/Zidovune/Nevirapine<br>Lamivudine/Stavudine/ Nevirapine<br>Tenofovir Disoproxil Fumarate /Efavirenz/ Emtricitabine | Unspecified | Combination of outlets / Convenience | USP or manufacturer's methods or in-house specifications | API content, API identification, Disintegration, Dissolution, Visual inspection, Related substances, Weight uniformity<br><br>*TLC and HPLC*<br><br>*Tier analysis:*<br>*Tier 1 : screening testing using the GPHF-Minilab*<br>*Tier 2 : samples failing Tier 1 and 10% samples not failing Tier 1 followed full pharmacopeial testing* | 17/2630 (0.6%) |

| Reference / country of collection | Active pharmaceutical ingredient (API) | Brand name | Outlet/ Sampling type | Reference specifications stassindard | Test (s) performed and main analytical technique | No. Failed n (%) |
|---|---|---|---|---|---|---|
| HPLC, High-performance liquid chromatography; IR, Infrared; UV, Ultraviolet; TLC, Thin Layer Chromatography; BP, British Pharmacopeia; USP, United Stated Pharmacopeia; API, Active Pharmaceutical Ingredient | | | | | | |


1 Penzak SR, Acosta EP, Turner M, *et al.* Analysis of Generic Nevirapine Products in Developing Countries. *J Am Med Assoc* 2003;**289**:2648–9. doi:10.1001/jama.289.20.2648-c

2 Penzak SR, Acosta EP, Turner M, *et al.* Antiretroviral Drug Content in Products from Developing Countries. *Clin Infect Dis* 2004;**38**:1317–9. doi:10.1086/383575

3 Ramachandran G, Perloff ES, Von Moltke LL, *et al.* Analysis of generic antiretroviral formulations manufactured in India. AIDS. 2004;**18**:1482–4. doi:10.1097/01.aids.0000131346.76289.27

4 Ciss M. Une démarche qualité pour le contrôle des médicaments: Cas des ARV. 22/03/2006 Pr M. - PDF Free Download. https://docplayer.fr/21057770-Laboratoire-national-de-controle-des-medicaments-une-demarche-qualite-pour-le-controle-des-medicaments-cas-des-arv-22-03-2006-pr-m.html (accessed 2 Jun 2020).

5 Chambuso MH, Ngassapa OD, Sayi JG, *et al.* Quality of antiretroviral drugs, stavudine and indinavir capsules available in the Tanzanian market. *Tanzania Med J* 2006;**21**:8–12. doi:10.4314/TMJ.V21I1.39202

6 WHO. Survey of the quality of antiretroviral medicines circulating in selected African countries. https://extranet.who.int/prequal/content/ (accessed 2 Jun 2020).

7 Sarr SO. Control of the Quality of Antiretroviral Medicines Used in Senegal. 2008.https://pubmed.ncbi.nlm.nih.gov/19626794/ (accessed 2 Jun 2020).

8 David Musoke. Assessment of the drug storage facilities and quality of generic co-formulation tablets (stavudine, lamivudine, nevirapine) at HIV/AIDS treatment centers in Uganda. https://www.researchgate.net/publication/289843470_Assessment_of_the_drug_storage_facilities_and_quality_of_generic_co-

formulation_tablets_stavudine_lamivudine_nevirapine_at_HIVAIDS_treatment_centers_in_Uganda (accessed 2 Jun 2020).

9 Munkombwe D. Quality analysis of some first-line HIV/AIDS medicines dispensed in Lusaka District Health facilities of Zambia. Published Online First: 16 November 2011.http://palevel.unza.zm/handle/123456789/897 (accessed 2 Jun 2020).

10 NASCOP. Post Market Survey of Antiretroviral Medicines in Kenya. https://drive.google.com/file/d/1KlPAstp8su82rS_bTWfMfmRSRDL93QbM/view (accessed 2 Jun 2020).

11 Chigunta MM. Quality analysis of selected Pediatric HIV/AIDS/TB Medicines in Livingstone District, Zambia. Published Online First: 4 February 2014.http://dspace.unza.zm:8080/xmlui/bitstream/handle/123456789/3188/Chigunta.pdf?sequence=1 (accessed 2 Jun 2020).

12 Christi Lane LAK. Cambodian Ministry of Health Takes Decisive Actions in the Fight against Substandard and Counterfeit Medicines. *Trop Med Surg* 2014;**02**. doi:10.4172/2329-9088.1000166

13 Wang T, Hoag SW, Eng ML, *et al.* Quality of antiretroviral and opportunistic infection medications dispensed from developing countries and Internet pharmacies. *J Clin Pharm Ther* 2015;**40**:68–75. doi:10.1111/jcpt.12226

14 Sapsirisavat V, Vongsutilers V, Thammajaruk N, *et al.* Pharmaceutical Equivalence of Distributed Generic Antiretroviral (ARV) in Asian Settings: The Cross-Sectional Surveillance Study – PEDA Study. *PLoS One* 2016;**11**:e0157039. doi:10.1371/JOURNAL.PONE.0157039

15 Kamangu EN, Mbinze JK, Mingu AM, *et al.* UV Visible Spectrophotometric Determination of the Quality of Antiretroviral Drugs Distributed in Kinshasa. *OALib* 2017;**04**:1–8. doi:10.4236/oalib.1102923

16 World Health Organization. Survey of the quality of selected antiretroviral medicines circulating in five African countries. Published Online First: 2017.https://extranet.who.int/prequal/content/ (accessed 2 Jun 2020).

17 Djobet MPN, Singhe D, Lohoue J, *et al.* Antiretroviral therapy supply chain quality control and assurance in improving people living with HIV therapeutic

outcomes in Cameroon. *AIDS Res Ther* 2017;**14**:19. doi:10.1186/s12981-017-0147-x

18 Wang X, Nutland W, Brady M, *et al.* Quantification of tenofovir disoproxil fumarate and emtricitabine in generic pre-exposure prophylaxis tablets obtained from the internet. *Int J STD AIDS* 2019;**30**:765–8. doi:10.1177/0956462419841144

19 Mziray S, Maganda BA, and … KM-BMCP, *et al.* Quality of selected anti-retroviral medicines: Tanzania Mainland market as a case study. *Springer*https://link.springer.com/article/10.1186/s40360-021-00514-w

**Supplementary file 7:** Failure rate per type of quality test performed in prevalence surveys

*Because of the limited number of samples tested for quality in the studies included in this review, the figures should not be interpreted as representative of the prevalence of specific SF antiretroviral medicines (please refer to the discussion section of the current paper for more details)*

| **Quality test** | **Failure Rate % (n/N)** |
|---|---|
| API content | 1.4% (14/1,034) |
| Dissolution | 1.3% (8/616) |
| Visual inspection of dosage units/non-comparative packaging analysis | 0.2% (6/3,256) |
| Impurity/Contaminant/Related substance | 0.0% (0/495) |
| Other physical analysis** | 0.5% (19/3,910) |
| Other chemical analysis* | 0.2% (5/2,830) |
| Unknown/Not detailed | 0.8% (1/133) |

**Includes content uniformity, bioavailability, identification of APIs, API semi-quantitation*

***Includes weight uniformity, weight variation, friability, hardness, disintegration, pH, microbiology, mass uniformity*

*Note: One sample may have been tested for one or more quality tests*

**Supplementary file 8:** Samples collected by type of outlet in prevalence surveys

*Because of the limited number of samples tested for quality in the studies included in this review, the figures should not be interpreted as representative of the prevalence of specific SF antiretroviral medicines (please refer to the discussion section of the current paper for more details)*

| **Type of outlet** | **Failure rate % (n/N)** |
|---|---|
| Private pharmacy | 28.0% (7/25) |
| Hospital/health centres | 19% (8/98) |
| Website | 7.7% (2/26) |
| Government outlets – others* | 6.3% (1/16) |
| Combination of outlets | 2.2% (29/1,302) |
| Ports of entry | 0.0% (0/2,200) |
| Manufacturer | 0.0% (0/17) |
| Non-governmental organization | 0.0% (0/7) |
| Wholesalers/importer/distributors | 0.0% (0/1) |
| Unknown | 19.0% (4/21) |
| **Total** | **1.4% (51/3,713)** |

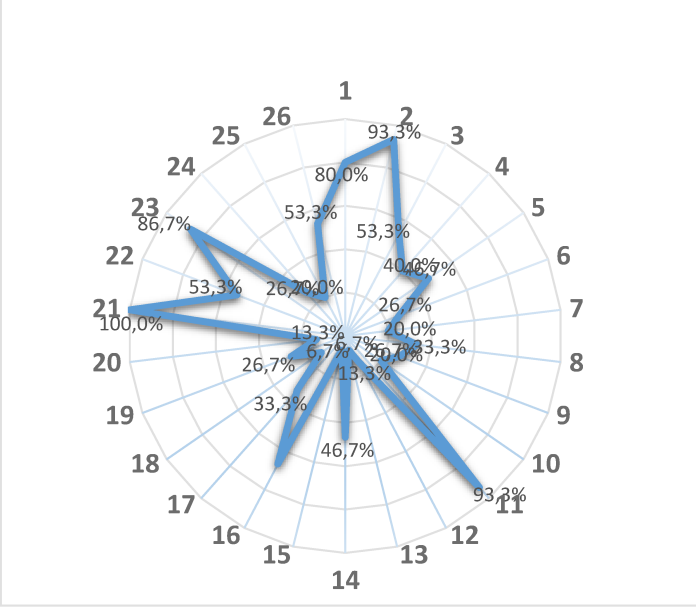
*included: *government pharmacies and other public health facilities*

**Supplementary file 9**: Failure rates by region of the stated manufacturer in prevalence surveys

*Because of the limited number of samples tested for quality in the studies included in this review, the figures should not be interpreted as representative of the prevalence of specific SF antiretroviral medicines (please refer to the discussion section of the current paper for more details)*

| **Continent** | **Failure Rate n/N (%)** |
|---|---|
| Americas | 14.3% (1/7) |
| Asia | 3.8% (9/238) |
| Europe | 0.0% (0/2) |
| Africa | 0.0% (0/2) |
| Unknown | 1.2% (41/3,464) |
| **Total** | 1.4% (51/3,713) |

**Supplementary file 10. Frequency of agreement with the 26 items of the MEDQUARG checklist of the 15 prevalence surveys**




*Definition of items: 1. Title/abstract/keywords 2. Introduction.*
*Methods (items 3-13): 3. Survey details 4. Definitions 5. Outlets 6. Sampling design 7. Samplers 8. Statistical methods 9. Ethical issues 10. Packaging 11. Chemical analysis 12. Method validation 13. Blinding. Results (items 14-20): 14. Outlets (actual) 15. Missing samples 16. Packaging and chemistry results 17. Category of poor quality medicine 18. State company and address as given on packaging 19. Sharing data with MRA 20. Dissemination. Discussion (items 21-24): 21. Key results 22. Limitations 23. Interpretation 24. Intervention. Declaration: 25. Conflict of interest 26. Funding.*

| No | Item | Penzak, S.R. et al, 2004 | M.H.S. Chambuso et al, 2006 | WHO, 2007 | Musoke. D et al, 2008 | Sarr, S. O. et al, 2008 | NASCOP, 2012 | Chigunta, M.M. et al, 2013 |
|---|---|---|---|---|---|---|---|---|
| 1 | Title/abstract/keywords | N | N | Y | Y | Y | N | Y |
| 2 | Introduction | Y | Y | Y | Y | Y | Y | Y |
| **Methods** | | | | | | | | |
| 3 | Survey details | N | N | Y | Y | N | Y | Y |
| 4 | Definitions | N | Y | N | N | N | Y | Y |
| 5 | Outlets | N | N | Y | Y | N | N | N |

| No | Item | Penzak, S.R. et al, 2004 | M.H.S. Chambuso et al, 2006 | WHO, 2007 | Musoke. D et al, 2008 | Sarr, S. O. et al, 2008 | NASCOP, 2012 | Chigunta, M.M. et al, 2013 |
|---|---|---|---|---|---|---|---|---|
| 6 | Sampling design | N | N | Y | N | N | N | Y |
| 7 | Samplers | N | N | Y | N | N | N | Y |
| 8 | Statistical methods | Y | N | N | Y | N | Y | Y |
| 9 | Ethical issues | N | N | N | Y | N | N | Y |
| 10 | Packaging | N | Y | Y | N | N | N | N |
| 11 | Chemical analysis | Y | Y | Y | Y | N | Y | Y |
| 12 | Method validation | N | N | Y | N | N | N | N |
| 13 | Blinding | N | N | Y | N | N | N | N |
| **Results** | | | | | | | | |
| 14 | Outlets | N | N | Y | Y | Y | N | N |
| 15 | Missing samples | N | N | N | N | N | N | N |
| 16 | Packaging and chemistry results | Y | Y | Y | N | N | N | Y |
| 17 | Category of poor-quality medicine | N | N | N | N | N | Y | N |
| 18 | State company and address as given on packaging | N | N | N | N | N | N | N |
| 19 | Sharing data with MRA | N | N | N | N | Y | Y | N |
| 20 | Dissemination | N | N | N | N | N | N | Y |
| **Discussion** | | | | | | | | |
| 21 | Key results | Y | Y | Y | Y | Y | Y | Y |
| 22 | Limitations | N | N | Y | N | N | Y | Y |
| 23 | Interpretation | Y | Y | Y | N | N | Y | Y |
| 24 | Intervention | N | N | N | N | Y | Y | N |
| **Other Information** | | | | | | | | |
| 25 | Conflict of interest | N | N | N | N | N | N | N |
| 26 | Funding | N | N | N | Y | N | Y | N |
| | Total score | **6** | **7** | **15** | **10** | **6** | **12** | **14** |
| | | **23.1%** | **26.9%** | **57.7%** | **38.5%** | **23.1%** | **46.2%** | **53.8%** |

Y : Yes, N : No

| No | Item | Krech. L.A et al, 2014 | Wang, T et al, 2015 | Sapsirisavat, V et al, 2016 | Djobet. M.P.N et al, 2017 | WHO, 2017 | Kamangu, E.N. et al 2017 | Wang, X et al, 2019 | Mziray S et al, 2021 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Title/abstract/keywords | Y | Y | Y | Y | Y | Y | Y | Y |
| 2 | Introduction | Y | Y | Y | Y | Y | Y | N | Y |
| **Methods** | | | | | | | | | |
| 3 | Survey details | N | N | Y | Y | Y | Y | N | N |
| 4 | Definitions | Y | Y | Y | N | N | N | N | N |
| 5 | Outlets | Y | Y | Y | N | N | Y | N | Y |
| 6 | Sampling design | N | N | Y | N | Y | N | N | N |
| 7 | Samplers | N | Y | N | N | N | N | N | N |
| 8 | Statistical methods | N | N | N | Y | N | N | N | N |
| 9 | Ethical issues | N | N | N | Y | N | N | N | Y |
| 10 | Packaging | N | N | N | Y | N | N | N | N |
| 11 | Chemical analysis | Y | Y | Y | Y | Y | Y | Y | Y |
| 12 | Method validation | N | N | N | N | N | N | N | Y |
| 13 | Blinding | N | N | N | N | N | N | N | N |
| **Results** | | | | | | | | | |
| 14 | Outlets | N | N | Y | Y | N | N | Y | Y |
| 15 | Missing samples | N | N | N | Y | N | N | N | N |
| 16 | Packaging and chemistry results | N | Y | Y | Y | Y | Y | N | Y |
| 17 | Category of poor-quality medicine | N | N | Y | Y | Y | Y | N | N |
| 18 | State company and address as given on packaging | N | Y | N | N | Y | N | N | N |
| 19 | Sharing data with MRA | Y | N | N | N | N | N | N | Y |
| 20 | Dissemination | N | N | N | N | N | N | N | Y |
| **Discussion** | | | | | | | | | |
| 21 | Key results | Y | Y | Y | Y | Y | Y | Y | Y |
| 22 | Limitations | Y | N | Y | Y | Y | N | Y | N |
| 23 | Interpretation | Y | Y | Y | Y | Y | Y | Y | Y |
| 24 | Intervention | Y | N | N | N | N | N | N | Y |
| **Other Information** | | | | | | | | | |

| No | Item | Krech. L.A et al, 2014 | Wang, T et al, 2015 | Sapsirisavat, V et al, 2016 | Djobet. M.P.N et al, 2017 | WHO, 2017 | Kamangu, E.N. et al 2017 | Wang, X et al, 2019 | Mziray S et al, 2021 |
|---|---|---|---|---|---|---|---|---|---|
| 25 | Conflict of interest | N | N | Y | N | N | N | Y | Y |
| 26 | Funding | N | Y | Y | Y | N | Y | Y | Y |
| | Total score | **10** | **11** | **15** | **15** | **11** | **10** | **8** | **15** |
| | | **38.5%** | **42.3%** | **57.7%** | **57.7%** | **42.3%** | **38.5%** | **30.8%** | **57.7%** |

Y : Yes, N : No

**Supplementary file 11: Description of identified recalls/alerts, seizures and case-reports of substandard and falsified antiretroviral medicines**

| Reference | Country | Date of incident | Type of publication | Information on the incidents |
|---|---|---|---|---|
| [1] | Unstated | Jan 1992 | Recall/Alert | USFDA urged AIDS buyers clubs to stop the sale and distribution of unauthorized versions of zalcitabine (dideoxycytidine, ddC). The amount of Zalcitabine ranged from no drug to twice the labeled amount. (Buyers clubs are groups that facilitate patient access to drugs purported to be useful for treatment of AIDS or associated conditions). |
| [2] | Zimbabwe | 2001 | Case report | A married student aged 33 years from Harare, Zimbabwe, studying in the UK, had started self-treatment with zidovudine tablets bought from a chemist in Zimbabwe. A month later, his CD4 T lymphocyte count and viral load were abnormal. He thus stopped taking the tablets and sent them for analysis. Analysis showed that the tablets contained no zidovudine. |
| [3] | Tanzania | Aug 2001 | Seizure | 3.5 tons of re-packaged medicines of various types, including fake preparations for treating AIDS , were seized on 1st of August 2001 in Dar es Salaam. "Two Korean citizens had reportedly done brisk business by selling their AIDS drug, brand named as 'mocrea' and another synthetic compound named 'kissometa'" which they claimed enhanced male potency that were imported illegally into Tanzania. |
| [4] | USA | 2002 | Recall/Alert | Falsified labels for Combivir Tablets were placed on two bottles of Ziagen and labels on another two bottles were suspect. Both medicines are used aspart of combination regimens to treat HIV infection. |
| [5] | Côte d'Ivoire | Nov 2003 | Recall/ Alert | The World Health Organization received information about the presence of a falsified triple antiretroviral combination product, Ginovir 3D capsules, in Côte d'Ivoire. According to the Agence Française de Sécurité Sanitaire des Produits de Santé, laboratory investigations of Ginovir 3D samples did not show the presence of lamivudine or indinavir; the capsules were found to contain 201 mg of zidovudine and 40 mg of stavudine per capsule, in addition to an non-identified substance |
| [6] | USA | Dec 2000 | Seizure | In 2000, AmerisourceBergen bought 52 bottles of falsified Retrovir, from a small Ohio wholesaler. The bottles were found during a routine inspection in 2001 at AmerisourceBergen's Orlando distribution center. By turning to the smaller wholesaler rather than buying directly from the drug's manufacturer, AmerisourceBergen saved about $8 per bottle on a product that costs nearly $300 a bottle, sales records showed. |
| [7] | Democratic Republic of the Congo | 2004 | Case report | The emergence of falsified antiretroviral drugs in Democratic Republic of Congo has prompted serious concerns among groups that advocate widespread distribution of these drugs in HIV-affected countries. According to Médecins Sans Frontières, fluvoxamine (an antidepressant) and cyclobenzaprine HCl (a |

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| | | | | muscle relaxant) had been labeled as either "Triomune" (a combination of stavudine, lamivudine, and nevirapine) or "Duovir" (a combination of zidovudine and lamivudine), the two commonly prescribed antiretroviral brands that are manufactured by Indian pharmaceutical company Cipla. |
| [8] | Developing Countries | Nov 2004 | Recall/ Alert | Lamivudine 150mg tablet from Cipla Ltd, Kurkumbh, blister pack of 10; and Lamivudine 150mg plus Zidovudine 300mg tablet, Cipla Ltd, Vikhroli, blister pack of 10- The two medicines (which are used in the treatment of AIDS) had been delisted by WHO in May this year due to non-compliance with international standards at the contract research organizations (CROs) hired by Cipla to conduct bioequivalence tests on the products. |
| [9] | Europe | Jun 2007 | Recall/ Alert | The European Medicines Agency (EMEA)issued a Press Release announcing the Europe-wide recall of Viracept (nelfinavir). This recall was initiated after Roche, the manufacturer, identified the presence of ethyl mesylate in some batches of Viracept. Ethyl mesylate is a genotoxic substance that is harmful to DNA. |
| [10] | USA | Apr 2007 | Recall/ Alert | Cases of misbranding cases of two 60-units bottles of Combivir Tablets. Combivir Tablets (in a legitimate bottle) is stated to contain 150 milligrams of lamivudine and 300 milligrams of zidovudine; however, the misbranded bottles of Combivir contained 300 milligram tablets of Ziagen. The falsified labels identified Lot No. 6ZP9760 with expiration dates of April 2010 and April 2009. Company tests have shown no problems with the medicine itself; both Ziagen and Combivir are authentic drug product. |
| [11] | Germany | 2009 | Recall/ Alert | In 2009, falsified versions of GlaxoSmithKline's Combivir (lamivudine and zidovudine) and Boehringer Ingelheim's Viramune (nevirapine) were discovered in the legal supply chain in Germany, Combivir in Bremen and Viramune on the island of Sylt in northern Germany. |
| [12] | UK | 2011 | Case report | Orifarm, a Danish supplier of parallel-imported and generic pharmaceuticals acknowledged that their supply of Truvada had been compromised by "the presence of counterfeits," reported Securing Pharma. Additionally falsified Viread (tenofovir) has been found in the UK market. MHRA believes that the affected batches contained genuine medication destined for Turkey, however the packaging was falsified. The reason for the substitution of fake packaging is unknown. |
| [13] | Denmark | Nov 2011 | Recall/ Alert | Orifarm said it took the decision to withdraw supplies of Truvada (emtricitabine and tenofovir disoproxil fumarate) - a combination HIV medicine originally developed and marketed by US drugmaker Gilead Sciences, because it has been compromised by the presence of falsified samples. |
| [14] | Kenya | Sep 2011 | Case report | In September 2011, nurses working in an MSF (Médecins Sans Frontières) HIV/AIDS treatment program in Nairobi found two batches of the drug Zidolam-N, a fixed dose combination of zidovudine, lamivudine, and nevirapine, to be molding, friable, and discolored. On close inspection of the suspected products, WHO confirmed that the drugs had been falsified |

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| [15] | Tanzania | Aug 2012 | Recall/ Alert | In August, a batch of an unspecified HIV medicine, produced by the Tanzania Pharmaceutical Industry (TPI), was immediately recalled and subjected to further testing, which revealed that it was falsified. 12,000 bottles in the fake ARV batch, 9,570 had so far been successfully recalled. |
| I[16] | USA | Jul 2012 | Seizure | "During an investigation, the FBI seized more than $16 million worth of second-hand prescription drugs, comprised of more than 33,000 bottles and more than 250,000 loose pills, kept in uncontrolled and sometimes egregious conditions by various defendants and their co-conspirators". These were drugs designed to treat various illnesses, including HIV, schizophrenia, and asthma |
| [17] | UK | 2014 | Recall/ Alert | "Gilead Sciences Limited is recalling the batches (KFBSD, KFBTD) of Viread 245 mg Film-Coated Tablets due to possible presence of silicone rubber. A failure of equipment used in the manufacture of the active pharmaceutical ingredient formulated in these medicinal product batches may have resulted in damage to silicone gaskets and silicone fragments entering the product in these recalled lots." |
| [18] | Nigeria | Jan 2014 | Recall/ Alert | "The National Agency for Food and Drug Administration and Control, NAFDAC, suspended the use of Tryonex, a brand of Antiretroviral, medicines in the country. This was due to concerns expressed by Treatment Action Movement, TAM, a coalition of HIV activists in Nigeria and other similar organisations."[…] "The package presentation is substandard, the labelling is amateurish, resembling the work of professional counterfeits and street drugs peddlers. Some of the labels were actually upside down with conflicting and incorrect instructions for use." […] "The drug literature, he noted, was also stuffed inside the same plastic pack as the ARVs, giving little assurance of hygienic handling of the tablets during packaging." |
| [19] | Zimbabwe | Aug 2015 | Recall/ Alert | According to Police Commissioner Charity Charamba, from Zimbabwe, 424,000 tablets of fake anti-retroviral drugs were recalled in the country |
| [20] | Colombia | Nov 2015 | Seizure | According to the Colombian authorities, the drugs seized in simultaneous operations on November 22, 2015 in houses located in the cities of San Cristobal, Ciudad Bolivar and Bosa were to be distributed in some 50 pharmacies located in the center, west, and south of Bogota. Fake drugs were treatments against HIV-AIDS . According to the investigation, traffickers had added dyes or iodine in some drugs. In other cases, expired medicines were re-labeled |
| [21] | France | 2016 | Recall/Alert | Recall of 2 batches of the specialty VIRAMUNE 400mg, prolonged-release tablet, box of 30cp (lot 559829B -expiry 04/2018; lot 560038A - expiry 06/2018). "This recall follows the discovery of the presence of blisters of a lot in the other lot box" |
| [22] | Colombia | Jul 2016 | Seizure | "On 27 July 2016, Colombian police arrested 10 people suspected of being part of a gang smuggling and counterfeiting medicines. Among the fake drugs, the authorities reported having seized treatments against cancer, HIV-AIDS, |

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| | | | | contraceptives, almost 18 000 units worth 800 million pesos, or about UD$260.000. This network would be located in Bogota, Cucuta and Medellin." |
| [23] | Argentina | Jan 2018 | Recall/Alert | The National Administration of Drugs, Foods and Medical Devices Argentina (ANMAT) alerted the population on the existence of falsified batches of the following medicinal specialties:<br>Apidra 100 U.I./ml Insulina Glulisina, SoloSta - Lot 5F 964A expired: 10/2018.<br>Kaletra Lopinavir/Ritonavir 200 mg/50mg - Lot 347789D expired 08/2018.<br>Reyataz atazanavir 300mg/30 capsule, lot 4C85179A, expired. ABR 2018. |
| [24] | Argentina | Jan 2018 | Recall/Alert | ANMAT alerted the population on the existence of falsified batches of the following medicinal specialties: ISENTRESS Raltegravir 400 mg, lot ARG0324/L026309. PERJETA Pertuzumab 420 mg/ 14 ml, lot H0109918. VIRORREBER 600 Efavirenz 600 mg, lot MEG35IK4 |
| [25] | Worldwide | Oct 2018 | Seizure | "Almost one million packages were inspected during the week of action (9 – 16 October), with 500 tons of illicit pharmaceuticals seized worldwide.These included anti-inflammatory medication, painkillers, erectile dysfunction pills, hypnotic and sedative agents, anabolic steroids, slimming pills and medicines for treating HIV, Parkinson's and diabetes." |
| [26] | Zambia | 2016 | Case report | "Health Minister, Chitalu Chilufya, reported to have endangered the lives of thousands of patients by purchasing low standard medicines from questionable sources. A report revealed that the Ministry of Health procured expired antiretroviral treatments and laboratory products in 2016." |
| [27] | USA | 2021 | Recall/Alert | The Janssen Pharmaceutical Companies of Johnson & Johnson recently announced that a falsified form of Symtuza (darunavir/cobicistat/emtricitabine/tenofovir alafenamide) has been discovered in three US pharmacies. |
| [28] | USA | 2021 | Recall/Alert | "Gilead Sciences became aware of tampered and falsified versions of Biktarvy® (bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg tablets) and Descovy® (emtricitabine 200 mg and tenofovir alafenamide 25 mg tablets) in the US. Distributors not authorized by Gilead to sell Gilead-branded medicine had sold these falsified medicines to pharmacies where genuine Gilead bottles were tampered with a counterfeit foil induction seal or label and contain incorrect tablets" |
| FDA, Food and Drugs Administration; US, United States; UK, United Kingdom; MHRA, Medicines and Healthcare products Regulatory Agency; HIV-AIDS, Human Immunodeficiency Virus- Acquired Immunodeficiency Syndrome | | | | |

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**Supplementary file 12: Description of identified recalls/alerts, seizures and case-reports of substandard and falsified antiretroviral related medical devices.**

| Reference | Country | Date of incident | Type of publication | Information on the incidents |
|---|---|---|---|---|
| [1] | Kenya | Dec 2011 | Recall/Alert | Kenya recalled one million HIV testing kits because of fears about their accuracy. “The WHO had raised an alert about the kit after finding half the test results could be wrong, said Shahnaz Sharif.” […]"About 50% of positives may have been reported as negative and 50% of negatives as positive." |
| [2] | India | 2005-2007 | Seizure | India seized around 140000 packs of HIV diagnostic test kits. Several cases are described:1/A lot of inconsistencies in the expiry and manufacture dates, number of kits, type of defect (substitution by Pregnancy test or resale of just past-expiry kits), 2/In 2007, a doctor claimed and sue the NACO (National AIDS Control Organization) for not solving the issue, and that some tests were still available. 3/The same doctor raised up a scandal because the kits were procured by the World Bank that tried to hide the issue and found ways to cover them (using CDC agents with link to NACO.) |
| [3] | France | Aug 2015 | Recall/Alert | The blotted membrane unit lot 1412BG006;1501BB001;1501BA001 may generate a higher number of false reactive results than specified on the Instruction for Use. |
| [4] | Europe | Jun 2016 | Recall/Alert | Recall of lots due to possible quality defects in the production process of the raw materials:<br>HIV15100013 (Exp.: 2017-08-31)<br>HIV16010011 (Exp.: 2017-12-31)<br>HIV16020005 (Exp.: 2018-02-28)<br>HCV15100013 (Exp.: 2017-10-31)<br>HCV16010008 (Exp.: 2018-01-31)<br>HCV16030007 (Exp.: 2018-03-31)<br>HBSG15100016 (Exp.: 2017-10-31)<br>HBSG16010012 (Exp.: 2018-01-31) |
| [5] | UK | Jul 2016 | Recall/ Alert | Recall of RightSign HIV 1.2.O Rapid Test Cassette- manufactured by Hangzhou Biotest Biotech Co Ltd: devices may give incorrect results that could lead to a misdiagnosis:<br>HIV14060001<br>HIV14060002<br>HIV14100001<br>HIV14100002<br>HIV15080003<br>HIV15110001<br>HIV16020005<br>HIV16050008 |
| [6] | UK | Sep 2016 | Recall/ Alert | “Alert Xpert® HIV-1 Viral Load, Catalog GXHIV-VL-CE-10 lot 1000034821 (cartridge lot 14001) and/or GXHIV-VL-CE-10 lot 1000036280 (cartridge lot 14002) have |

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| | | | | experienced cartridge performance issues that manifest as abnormal PCR amplification curve patterns, which can yield invalid results (the most common outcome), or much less commonly, inaccurate quantification of HIV-1 RNA when using this test." |
| [7] | Singapore | Jun 2017 | Recall/Alert | The Singapore's Health Sciences Authority (HSA) stated that nine lots (SD Biloline HIV Ag/Ab combo kits , all lots from Feb 2016 up to May 2017) of the kits were recalled by the Korea based manufacturer, Standard Diagnostic Inc. due to their reduced sensitivity. According to the manufacturer, when a patient is in the early window period, the lower sensitivity of the affected lots may reduce detection with the possibility of a false negative result for this subset of patients. |
| [8] | UK | Aug 2017 | Recall/ Alert | Recall of Abbott Realtime HIV-1 assay with the lots : 473470;474215;474890,475025,475532,475694,476172,476356,476736,476951,476139 exhibit a higher than expected rate of error codes due to controls out of range or internal control failures, misquantitation, and the potential to not detect HIV |
| [9] | Guyana | Mar 2020 | Recall/ Alert | WHO was informed that at least 8,240 falsified rapid diagnostic tests to detect HIV-1/2 were distributed in Guyana at end-user level. The product was Uni-Gold™ HIV and claimed to be manufactured by Trinity Biotech plc. Genuine lot numbers were HIV7120026 and HIV6120030 |
| [10] | Kenya | Oct 2021 | Recall/ Alert | Unapproved HIV self-testing kits in the Kenyan market. There were fears that a number of people could be accessing unapproved and substandard kits in some private health facilities, with possibility of wrong HIV test results. |
| US, United States; UK, United Kingdom; ; MHRA, Medicines and Healthcare products Regulatory Agency; HIV-AIDS, Human Immunodeficiency Virus-Acquired Immunodeficiency Syndrome; CDC, Centers for Disease Control and Prevention. | | | | |

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## Supplementary file 13. Other articles on antiretroviral medicines quality included in the review

| Title | First author | Year |
|---|---|---|
| Determination of Azidothymidine and Its Degradation Product Thymine in Pharmaceutical Dosage Forms by HPLC and HPTLC Densitometry [1] | Tomankova. H | 1990 |
| Application of LC-NMR and LC-MS to the identification of degradation products of a protease inhibitor in dosage formulations [2] | Peng, S.X. | 1999 |
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