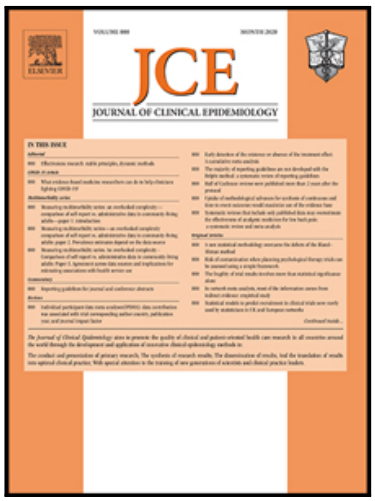

Acquired HIV drug resistance mutations on first-line antiretroviral therapy in Southern Africa: Systematic review and Bayesian evidence synthesis

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What is new?

- As many Southern African countries transition to dolutegravir-based antiretroviral therapy, there is a concern that patients who have been treated with NRTIs for a long period may have acquired resistance to NRTI, and then may be in situation of functional monotherapy when switched to dolutegravir-based antiretroviral therapy.
- We systematically reviewed studies assessing acquired drug resistance to NRTIs in Southern Africa among patients failing first-line ART and developed an innovative Bayesian evidence synthesis model to estimate the occurrence of several drug resistance mutations accounting for different study designs, regimens and treatment durations.
- We found that drug resistance mutations to NRTIs are common in patients failing first-line ART in Southern Africa, including mutations conferring high-level resistance to NRTIs that will be commonly combined with dolutegravir in the new regimen.
- We conclude that many patients failing an NNRTI-based ART may switch to a dolutegravir-based ART with compromised NRTIs, which could impair the long-term efficacy of ART in Southern Africa.

Acquired HIV drug resistance mutations on first-line antiretroviral therapy in Southern Africa: Systematic review and Bayesian evidence synthesis

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Abstract

Objective: To estimate the prevalence of NRTI and NNRTI drug resistance mutations in patients failing NNRTI-based ART in Southern Africa.

Study design: We conducted a systematic review to identify studies reporting drug resistance mutations among adult people living with HIV (PLWH) who experienced virological failure on first-line NNRTI-based ART in Southern Africa. We used a Bayesian hierarchical meta-regression model to synthesize the evidence on the frequency of eight NRTI- and seven NNRTI-DRMs across different ART regimens, accounting for ART duration and study characteristics.

Results: We included 19 study populations, including 2,690 PLWH. Patients failing first-line ART including emtricitabine or lamivudine showed high levels of the M184V/I mutation after two years: 75.7% (95% Credibility Interval [CrI] 61.9%-88.9%) if combined with tenofovir, and 72.1% (95% CrI 56.8%-85.9%) with zidovudine. With tenofovir disoproxil fumarate, the prevalence of the K65R mutation was 52.0% (95% CrI 32.5%-76.8%) at two years. On efavirenz, K103 was the most prevalent NNRTI resistance mutation (57.2%, 95% CrI 40.9%-80.1%), followed by V106 (46.8%, 95% CrI 31.3%-70.4%).

Conclusions: NRTI/NNRTI drug resistance mutations are common in patients failing first-line ART in Southern Africa. These patients might switch to dolutegravir-based regimen with compromised NRTIs, which could impair the long-term efficacy of ART.

Keywords: HIV, HIV drug resistance, ART, Southern Africa, Systematic review, Meta-analysis.

Word count: 199

1. Introduction

In 2014, UNAIDS communicated its goal of ending the AIDS epidemic as a public health threat by 2030 [1]. The strategy to achieve this objective involved stepping up testing and antiretroviral therapy (ART) in low and middle-income countries. In the last two decades, first-line ART consisted of a non-nucleoside reverse-transcriptase inhibitor (NNRTI) combined with two nucleos(t)ide reverse transcriptase inhibitors (NRTI) in most of these countries. For many NNRTIs, a single mutation will lead to high-level drug resistance, for example, the K103N mutation [2]. The combination of this low genetic barrier of NNRTI and their widespread use has lead to a continuous increase of pre-treatment drug resistance (PDR) to NNRTIs [3,4], which has exceeded the WHO threshold of 10% in Southern Africa [5]. Several countries in the region are therefore transitioning from the NNRTI based first-line triple therapy towards an integrase-strand-transfer-inhibitor (InSTI) based first-line regimen. WHO recommends TLD, a fixed-dose combination of tenofovir, lamivudine and dolutegravir (DTG) [6].

Among people living with HIV (PLWH) transitioning to DTG-based therapy, those with unsuppressed viral load are likely to have acquired resistance to NNRTIs or NRTIs. As NRTI-resistance reduces the activity of the NRTI backbone of DTG-based regimens, PLWH switching with pre-existing NRTI resistance are at higher risk of DTG-failure and of developing DTG-resistance. A cross-sectional survey in South Africa showed that 83% of patients failing NNRTI-based treatment had the M184V/I mutation, and over half the patients developed K65R, both of which confer resistance to NRTIs [7]. The risk of developing drug resistance mutations (DRMs) depends on several factors, including the ART regimen used and its duration [8].

In contrast to transmitted drug resistance, only a few studies have reported the prevalence of acquired drug resistance mutations in patients failing first-line ART in Southern Africa [5]. Most studies of acquired drug resistance (ADR) were performed in Europe or North America, where subtype B is most prevalent, while most HIV infections in Southern Africa are caused by subtype C [9,10]. In-vitro studies suggest that different subtypes might lead to different rates of ADR [11–13].

The few studies of ADR from Southern Africa and other resource-limited settings are heterogeneous, for example, regarding ART regimens or treatment duration. The heterogeneous nature of these studies makes summarizing and interpreting the evidence regarding ADR difficult. To address this challenge, we performed a systematic review and Bayesian evidence synthesis of studies reporting frequencies of drug resistance mutations in patients failing first-line ART in Southern Africa, a region heavily affected by HIV [14].

2. Methods

2.1 Literature search

We searched seven bibliographic databases from inception, including Embase and Medline, using terms for “HIV” AND “antiretroviral therapy” AND “drug-resistance mutations” AND “Southern Africa”. Appendix A provides details on the literature search. We performed the final search on Oct 9 2020, and de-duplicated references in EndNote (version 18.0.0). We registered this review in the International Prospective Register of Systematic Reviews (PROSPERO, No. CRD42017076406) [15].

2.2 Inclusion criteria

We searched for studies from Southern African countries in adult (15 years or older) PLWH on NNRTI-based first-line ART who were at least three months on treatment and experienced virological failure. The results of at least ten genotypic resistance tests covering all major single mutations listed in the Stanford HIV drug resistance database had to be reported [16]. First, FG and AH assessed articles based on their title and abstract. Second, AH and either FG or MLR assessed potentially eligible studies based on the full text. We compared the results of full-text screening and reached a consensus on eligibility by discussion.

2.3 Data extraction

We extracted details on study populations and settings, study year, the number of patients tested for viral load and with virological failure, and the time spent on ART. We recorded the definition of failure, i.e. the viral load threshold and the number of measurements required, and the first-line ART regimen. We extracted data on amino-acid substitutions commonly associated with drug resistance and referred to them as drug resistance mutations. We grouped resistance mutations by locus (for example, M184I/V). We defined the year of study as the year of the analysis, the year enrollment ended, or by the ‘sampling date’ recorded in GenBank [17]. If studies reported stratified data (for example, by country or level of urbanization), we extracted the data separately.

2.4 Bayesian evidence synthesis

We developed a hierarchical meta-regression model to estimate the prevalence of eight different NRTI mutations: K65N/R, M184I/V, M41L, D67N/G/E, K70E/G/R, L210W, T215F/I/N/S/Y, K219D/E/N/Q/R. Figure 1 and Appendix B detail the model structure. The model includes a random effect to account for study-level heterogeneity and a random effect at the mutation level. Our model accounts for the effect of both treatment duration and antiretroviral regimen on the prevalence of individual resistance mutations. To reflect that resistance is usually acquired during treatment failure, we developed a function that converts time on ART to time on failure (see Section 1.1 of Appendix B). We considered that time to acquiring a mutation was exponentially distributed, thus assuming a risk of developing a DRM is constant over time on failure. We examined the effect of different NRTI drugs on the risk of developing a DRM. We report model estimates of the prevalences of the seven major NRTI DRMs at baseline (treatment start, corresponding to the intercept of the regression model) and after two years. We opted for weakly informative prior distributions [18]. Appendix B reports the model equations and the prior distributions.

Figure 1. Bayesian hierarchical model adjusting for the different levels of heterogeneity.

We considered five NRTI drugs: didanosine (ddI), emtricitabine/lamivudine (FTC/3TC), tenofovir disoproxil fumarate (TDF), stavudine (d4T), and zidovudine (ZDV). As NRTI backbones mainly comprise either ddI or FTC/3TC and TDF, d4T, or ZDV, there were strong correlations between the drugs. We dealt with multicollinearity by selecting the covariates with the strongest effects first. In a sensitivity analysis, we also ran the model with all covariates. We imputed the time on ART in three studies [19–21] that did not report it, assuming that the missing ART durations followed a gamma distribution with mean and variance calculated from the observed ART durations in the other studies.

We also ran the model after discarding these three studies to assess the impact of data imputation (see Appendix B).

We also estimated the prevalence of any of six thymidine-analogue mutations (TAM), i.e. M41L, D67E/G/N, K70E/G/R, L210W, T215F/I/N/S/Y, or K219Q/E. As only a few studies reported the prevalence of any TAM, we adopted a method that estimated the correlation between the six TAMs (using results from the nine studies reporting the prevalence of the single TAMs and the prevalence of any TAM), assuming a multivariate Bernoulli distribution. We used this estimate to calculate the prevalence of any TAM (see Appendix B). Finally, we applied the same model to estimate the prevalence of seven NNRTI mutations (K101E/H/P/Q, K103N/R/S, V106A/I/M, V108I, Y181C/I/V, Y188C/H/L, G190A/E/R/S) as for the NRTI DRMs. We report estimates of DRM prevalence after two years of efavirenz (EFV) or nevirapine (NVP)-based regimens. The baseline prevalence of NNRTI DRMs was not reported because EFV and NVP select for the same NNRTI DRMs, which prevents the model from providing reliable estimates.

All Analyses were performed in a Bayesian framework using the *rstan* package in R (version 4.1.1). Multi-level Bayesian meta-analyses are particularly well-suited when the number of studies is small, as they allow to better incorporate the uncertainty on the between-study variance [22].

2.5 Risk of bias

Two of us (AH, ME) independently assessed study designs to gauge the representativeness of the patients for whom HIV genotypes were available. We calculated the percentage among patients with virological failure who had HIV genotypes. We considered studies at high risk of selection bias if i) genotyping rates were low (<50% of patients with failure were successfully genotyped); ii) there were relevant differences between the characteristics of genotyped and non-genotyped patient groups or iii) there was no clearly defined source population for patients to be genotyped. In a sensitivity analysis, we removed studies fulfilling one or more of these criteria and reran the analyses to examine the effect these studies had on the results (see Appendix B).

3. Results

3.1 Selection and characteristics of studies

Our initial search produced 8,534 articles; 3,462 were duplicates (Figure 2). We further excluded 4,836 papers based on title and abstract. We read the full texts of the remaining 236 articles. Of these, 18 studies were eligible, with 19 unique study populations from South Africa (13 studies), Botswana (1), Lesotho (1), Malawi (1), Mozambique (1), Tanzania (1), and Zambia (1) [7,19–21,23–34]. Most study populations were from urban settings.

Figure 2. PRISMA flow-chart of inclusion of studies and populations in the systematic review.

Table 1 summarizes the study samples, the numbers of patients included, and their characteristics. Most studies defined virological failure as a viral load >1000 copies/ml, either as a single measurement or confirmed by a second measure, as recommended by the WHO [6]. The most commonly used NRTI combinations were FTC/3TC with TDF (45% of patients), d4T (34%), or ZDV (17%). These NRTI drugs were mostly combined with EFV (76%) or NVP (23%). Of 3,915 patients with virological failure, 69% (2,690) had HIV genotype data available. In most study populations (11/19, 58%), the percentage of patients with virological failure with information on the HIV genotype was above 90%. Three large studies are responsible for the gap between the numbers of PLWH with virological failure and the number with genotype data. A national survey in South Africa [7] included 1,033 patients but obtained genotypes only for 788 (76.3%), and two other studies in South Africa [31,32], where only a subsample of the patients failing first-line ART had genotyping of HIV performed. Appendix C provides a detailed description of each study population.

Table 1. Characteristics of the 19 study samples included in the systematic review.

Screening of virological failure and genotyping	
Total No. of patients with virological failure	3915
No. of patients with genotype data	2690 (69%)
Median (range) number of patients with virological failure	102 (31-1033)
Median (range) number of patients with HIV genotype	68 (19-788)
Median (range) percent patients with HIV genotype among patients with virological failure	93% (10-100%)
Characteristics of patients	
NRTI regimen, proportion of patients	
TDF + FTC/3TC	44.7%
d4T + FTC/3TC	34.4%
ZDV + FTC/3TC	17.3%
Other or missing	3.6%
NNRTI regimen, proportion of patients	
EFV	76.4%
NVP	23.1%
Other or missing	0.5%
Median (range) time on ART (months)	29 (5-96)
Characteristics of studies	
Median (range) study year	2012 (2004-2018)
Definition of virological failure, number of studies (total patients)	
Confirmed >1000 copies/mL	7 (1530)
Single value >1000 copies/mL	7 (700)
Value >5000 copies/mL	3 (292)
Single value >400 copies/mL	1 (94)
Confirmed >80 copies/mL	1 (74)
Country, number of studies (total patients)	
Botswana	1 (23)
Lesotho	1 (74)
Malawi	1 (237)
Mozambique	1 (61)
South Africa	13 (2206)
Tanzania	1 (21)
Zambia	1 (68)
Urbanization, number of studies (total patients)	
Urban	9 (673)
Rural	6 (1006)

Both	4 (1011)

3.2 Prevalence of acquired NRTI resistance mutations

We found a variable prevalence of NRTI DRMs after two years of either FTC/3TC and TDF or FTC/3TC and ZDV (Figure 3A). The prevalence at baseline for NRTI DRMs was low, ranging from 1% to 8.4%. The use of FTC/3TC was associated with high levels of the M184V/I mutation. The prevalence was 75.7% (95% credible interval [CrI] 61.9%-88.9%) after two years on FTC/3TC combined with TDF and 72.1% (95% CrI 56.8%-85.9%) on FTC/3TC combined with ZDV. When FTC/3TC was combined with TDF, there was a substantial increase in the K65N/R mutation: from 2.1% (95% CrI 0.7%-3.5%) at baseline to 52% (95% CrI 32.5%-76.8%) after 2 years. The increases over time in the levels of K65N/R and M184V/I on ART are displayed in Figure 3B and Figure 3C. In contrast, the prevalence of each of the six TAM mutations after two years of FTC/3TC combined with either TDF or ZDV were moderate, ranging from 1.6% to 24.5%. Finally, when the six TAM mutations were combined into a single outcome, the model showed a higher risk of developing any of the six TAMs when FTC/3TC was combined with ZDV rather than TDF: 44.5% (95% CrI 34.5%-58.5%) versus 28.5% (95% CrI 21%-41.4%) after two years, suggesting some correlation between the different TAMs (see Section 2.3 of Appendix B).

Figure 3. Prevalence of nine NRTI drug resistance mutations by first-line regimen. Panel A: baseline prevalence and prevalence after 2 years of treatment according to NRTI use. Panel B: Prevalence of the K65 mutation over time. Panel C: Prevalence of the M184 mutation over time. Points and vertical lines: median and 95% credibility intervals of baseline prevalence (black), prevalence after 2 years on FTC/3TC + TDF (red) or FTC/3TC + ZDV (blue). Shaded area: 95% credibility interval over time.

3.3 Prevalence of acquired NNRTI resistance mutations

Our model also estimated highly variable prevalences of the seven NNRTI DRMs after two years of either EFV- or NVP-based regimens (Figure 4A). K103N/R/S was the most frequent NNRTI DRM, with a high prevalence after two years of EFV-based (57.2%, 95% CrI 40.9%-80.1%) or NVP-based regimens (42.2%, 95% CrI 22.4%-72.3%). Other NNRTI DRMs with prevalence estimates over 20% included V106A/I/M, Y181C/I/V, and G190A/E/R/S. Of note, the model estimated a higher prevalence of the Y181 mutations after the use of NVP (38.7%, 95%CrI 19.3%-64.4%) than with EFV (17.5%, 95%CrI 9.2%-34.6%). The increase over time of ART of K103N/R/S and Y181C/I/V is displayed in Figure 4B-C, respectively. Appendix B gives estimates of the prevalence of the NRTI/NNRTI DRMs at baseline and after 2 and 3 years of ART.

Figure 4. Prevalence of seven NNRTI drug resistance mutations. Panel A: Prevalences after 2 years on either EFV- or NVP-based regimen. Panel B: Prevalence of the K103 mutation over time. Panel C: Prevalence of the Y181 mutation over time. Points and vertical lines: median and 95% credibility intervals of baseline prevalence (black), prevalence after 2 years on EFV (orange) or NVP (green). Shaded area: 95% credibility interval over time. In contrast to Figure 3, the Panel A do not report baseline prevalence because EFV and NVP select for the same NNRTI DRMs, which prevents the model from providing reliable estimates.

3.4 Risk of bias and sensitivity analyses

We identified five studies at high risk of selection bias [26,29,31,32,35]. Four had proportions of genotyping below 50% [29,31,32,35]. Three of these, by design, only genotyped a subsample of infections [31,32,35]. One study [31] reported that every third patient was systematically sampled for genotyping; however, the number of infections genotyped was substantially lower (10.1% rather than the expected 33.3%, Appendix C). Genotyping in the second study [32] depended on the

availability of residual plasma. In the third study [35], only a subsample of the patients, which were said to be representative of the cohort, were selected for sequencing due to financial constraints. Finally, one study [26] lacked a clearly defined source population. It was based on referrals of patients with suspected first-line treatment failure at a University Teaching Hospital. Estimating the prevalence of the eight NRTI DRMs and seven NNRTI DRMs excluding the studies at high risk of bias showed that most estimates were very similar to the main analysis but with larger uncertainty (Appendix B). Similarly, removing the studies with missing ART duration (rather than imputing it) or using all the covariates on NRTI use (rather than including a selection step) did not substantially affect the results (see Appendix B and Figures B4 and B5).

4. Discussion

This systematic review and Bayesian meta-analysis provide estimates of emerging DRMs in patients failing first-line antiretroviral therapy in Southern Africa. Using a hierarchical structure and adjusting for the use of different drugs, the model estimates the major NRTI/NNRTI mutations while appropriately accounting for between-study heterogeneity. The most frequently acquired mutations among patients with virological failure after two years of ART were M184, K65 and K103 (prevalence 52% to 76%). Of note, K65 and M184 confer high-level resistance to FTC/3TC and TDF, the two NRTI backbones that are usually combined in DTG-based regimens. The model also estimated that 28% to 44% of patients failing an NNRTI-based regimen had at least one TAM.

The TenoRes study assessed the levels of NRTI resistance across regions of the world after the failure of NNRTI + FTC/3TC + TDF [36]. For Southern Africa, it estimated high levels of both M184 and K65 mutations (59% and 56%, respectively), in line with our study. The study found lower levels of M184 and K65 mutations in Europe (34% and 20%) or North America (42% and 22%) [36]. The authors argued that these differences in NRTI DRM levels might be driven by the higher frequency of viral load monitoring in Europe and North America. Also, in line with our study, the TenoRes study showed that Southern Africa is the only region with a similar prevalence of M184 and K65 mutations. In contrast, a higher prevalence of M184 mutations was observed in all other regions. Subtype C is most prevalent in Southern Africa and in-vitro studies suggest that the K65 mutation might be more likely to emerge in subtype C compared to other subtypes due to a nucleotide template-based mechanism [11–13]. This may have contributed to the high frequency of K65 in the included studies.

The high prevalence of the K65N/R and M184I/V mutations means that 39.4% (corresponding to 52.0% times 75.7%) to 52.0% of PLWH failing first-line ART that includes TDF and 3TC might have both, depending on the correlation between the two mutations. In its new guidelines, the South African Department of Health recommends switching patients failing a first-line regimen that includes FTC/3TC and TDF to DTG combined with FTC/3TC and ZDV to have at least one fully active

NRTI [37]. However, given the toxicity and side effects of ZDV and no fixed-dose combination combining DTG and ZDV, TDF might be preferred over ZDV [38]. In this context, our results show that up to half of these patients will start a DTG-based regimen without a fully active NRTI. The DAWNING trial [39] showed that DTG-based ART is effective in second-line ART, provided it is combined with at least one fully active NRTI. However, it is uncertain whether a functional DTG monotherapy, i.e. DTG with no fully active NRTIs, will be effective. Concerns on the efficacy of functional DTG-monotherapy have been raised by studies showing high failure rates with DTG-monotherapy [40]. The efficacy of functional DTG-monotherapy might be higher than DTG-monotherapy, as some residual NRTI activity may still exist even in case of resistance. This assumption is supported by the EARNEST and NADIA studies, where the presence of NRTI resistance did not impair virological response to second-line regimen [38,41].

Our meta-analysis also shows that TAM mutations are present at a moderate level among people failing a NNRTI-based first-line regimen. Interestingly, in several studies, the detection of NRTI resistance and particularly of TAMs before starting second-line ART was associated with better virological suppression, possibly because patients who developed resistance may, on average, have better adherence [42,43]. The large-scale switch to DTG-based ART should be accompanied by longitudinal, real-world studies of virological failure and drug resistance monitoring.

We observed a high prevalence of the K103 mutation (57% after two years on EFV, 42% on NVP), conferring high resistance to both EFV and NVP. Several Southern African countries recommend adherence support in patients on failing NNRTI-based regimens to achieve viral suppression before switching to DTG. In the case where patients remain unsuppressed after six months, these patients should nevertheless switch to DTG. The high level of NNRTI-resistance harbored by these patients questions the efficacy of such a strategy. Indeed, prolonging a failing regimen might increase the risk of accumulation of NRTI DRMs, potentially impairing the efficacy of a future switch to DTG. Among the other NNRTI drug resistance mutations, Y181C/I/V is of particular concern. The estimated prevalence of this mutation was about 17% and 39% after two years of EFV and NVP, respectively,

reflecting the higher impact of Y181 on NVP, as previously observed [44]. This mutation also confers resistance to the newer generation of NNRTIs, such as etravirine and rilpivirine. Finally, the high prevalence of V106 mutation found (46.8% after two years on EFV) confirms the higher propensity of subtype-C to acquire this mutation, as observed in in-vitro studies [45]. In-vitro observation could however not explain the lower prevalence of V106 mutation when using NVP (13.4% after two years).

Most previous reviews of HIV drug resistance focused on transmitted drug resistance rather than the resistance that was likely acquired during ART [46], and earlier reviews of ADR on failure rates, CD4-positive lymphocyte counts, and the prevalence of drug resistance mutations overall [47,48], or a subset of mutations [36,49,50]. Our study provides estimates of all relevant ADR mutations according to the drugs used for the whole region of Southern Africa, the region with the highest burden of HIV. To our knowledge, this is the first meta-analysis of this literature that uses a hierarchical structure jointly estimating the respective effects of multiple drugs on the emergence of multiple DRM.

Our review has several limitations. Many of the included studies were based on patients attending one or few outpatient clinics. We carefully assessed the likely representativeness of the patients undergoing HIV genotyping. Still, even if results reflect the situation in these clinics, they may not be representative of all patients who fail first-line ART in the region. In particular, loss to follow-up might underestimate the proportion of patients with resistance, in the case where loss to follow-up is associated with a higher risk of DRM. Indeed, the between-study heterogeneity was large, and decision-makers should consider the studies most relevant to their settings, as well as the regional data. Many factors may have introduced heterogeneity, including differences between study populations, their levels of adherence, the first-line regimen used, and the time spent on a failing regimen. One main strength of our approach is that the hierarchical structure of the model adjusted for regimen and time spent on a failing regimen, thereby addressing two major sources of heterogeneity, but some residual heterogeneity remains. Of note, in our sensitivity analyses, the likely risk of selection bias did not appear to influence estimates. Finally, we attempted to assess pre-

treatment NRTI mutations, but the wide credibility intervals illustrate the difficulty to disentangle pre-treatment from acquired drug NNRTI resistance.

Although we searched for studies from all over Southern Africa, most of the data included in our analysis were from South Africa. South Africa is one of few countries in the regions that have implemented routine viral load monitoring in patients on ART, and routine viral load monitoring is associated with a reduced probability of drug resistance [50]. Therefore, the overrepresentation of South African studies in our meta-analysis might underestimate the frequencies of the different DRMs in the rest of Southern Africa.

In conclusion, our analysis demonstrates that in Southern Africa, many patients failing first-line ART have DRMs, with important implications for the likely future transmission of drug resistance, the choice of second-line regimen, and the large-scale transition to DTG-based first-line ART. These implications are particularly pertinent to settings where routine viral load and drug resistance testing is not routinely available [51].

5. Additional information

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6. Appendix: Supplementary data

Supplementary materials are available online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author. A research replication archive is accessible at https://github.com/anthonyhauser/ADR-meta-analysis.

Author contributions.

ME, RK, and FG conceived the study, AH and JR developed the Bayesian model. FG and AH searched and collected the literature. FG, AH, and MR performed the screening of publications. AH and JR performed the statistical analysis. ME, FG, and AH analyzed the risk-of-bias. All authors interpreted the results. AH wrote the first draft of the manuscript, which was revised by JR, RK and ME. All authors provided comments on the manuscript.

Potential conflicts of interest.

The authors have no conflict of interest to declare.

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Fig. 1.

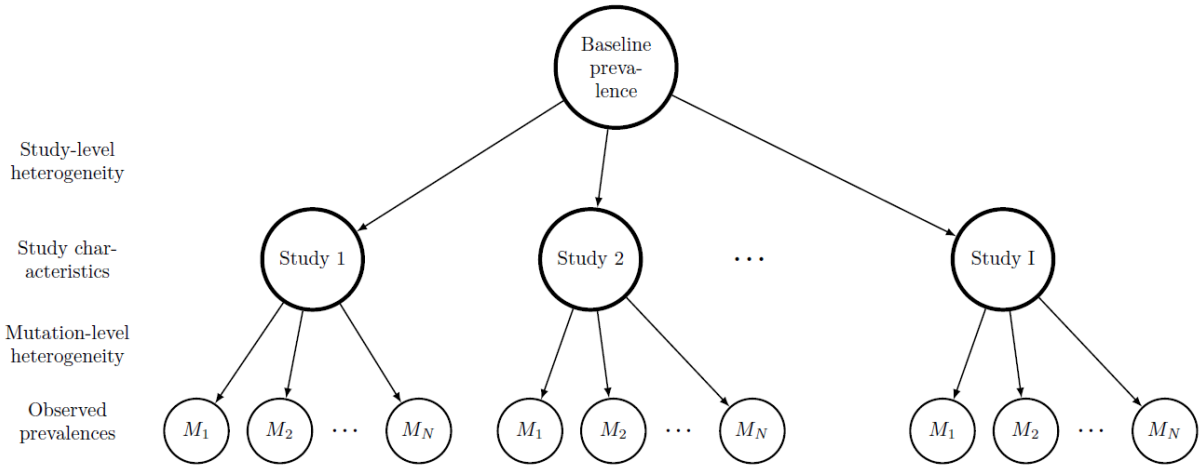

Fig. 2

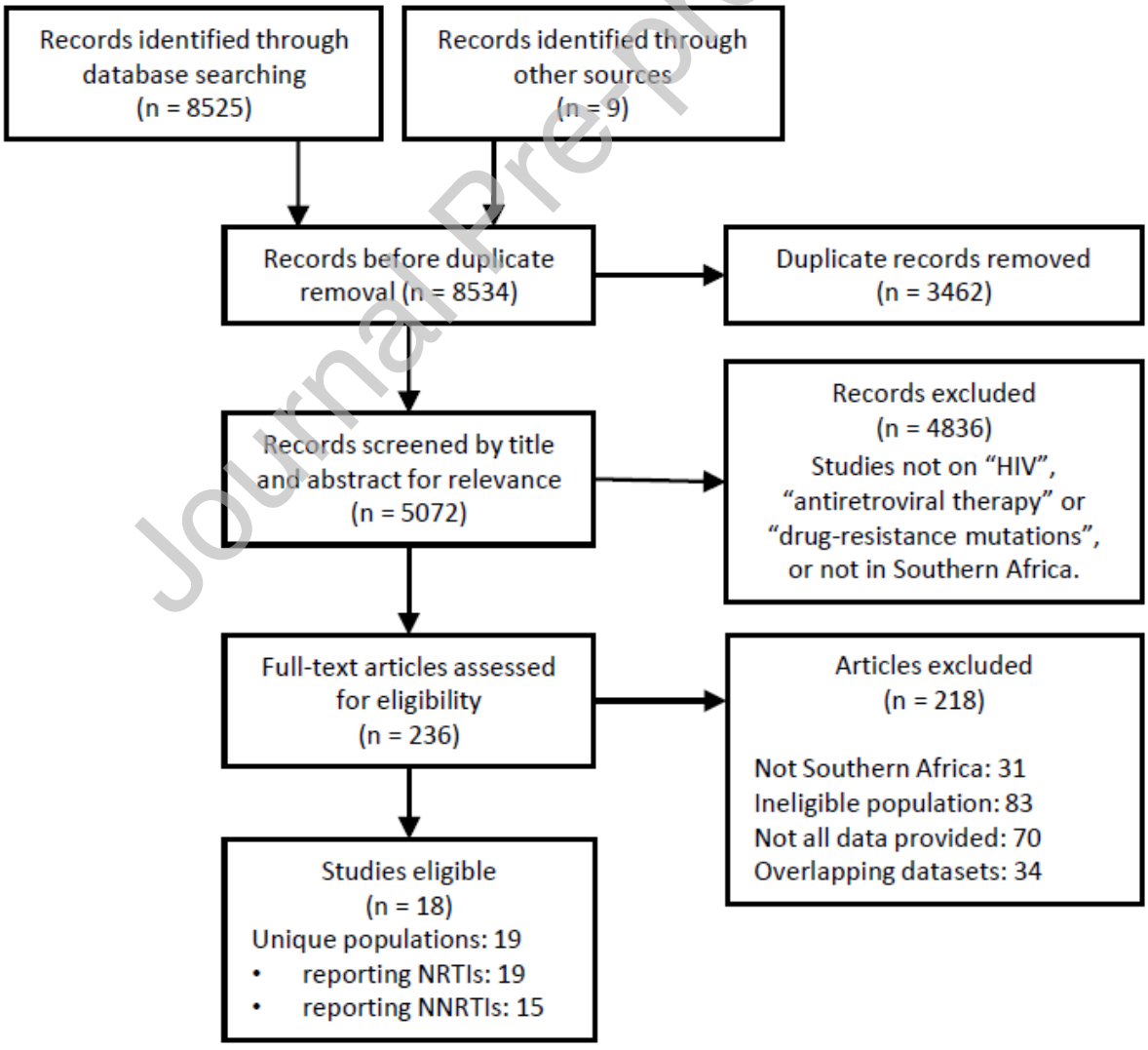

Fig. 3

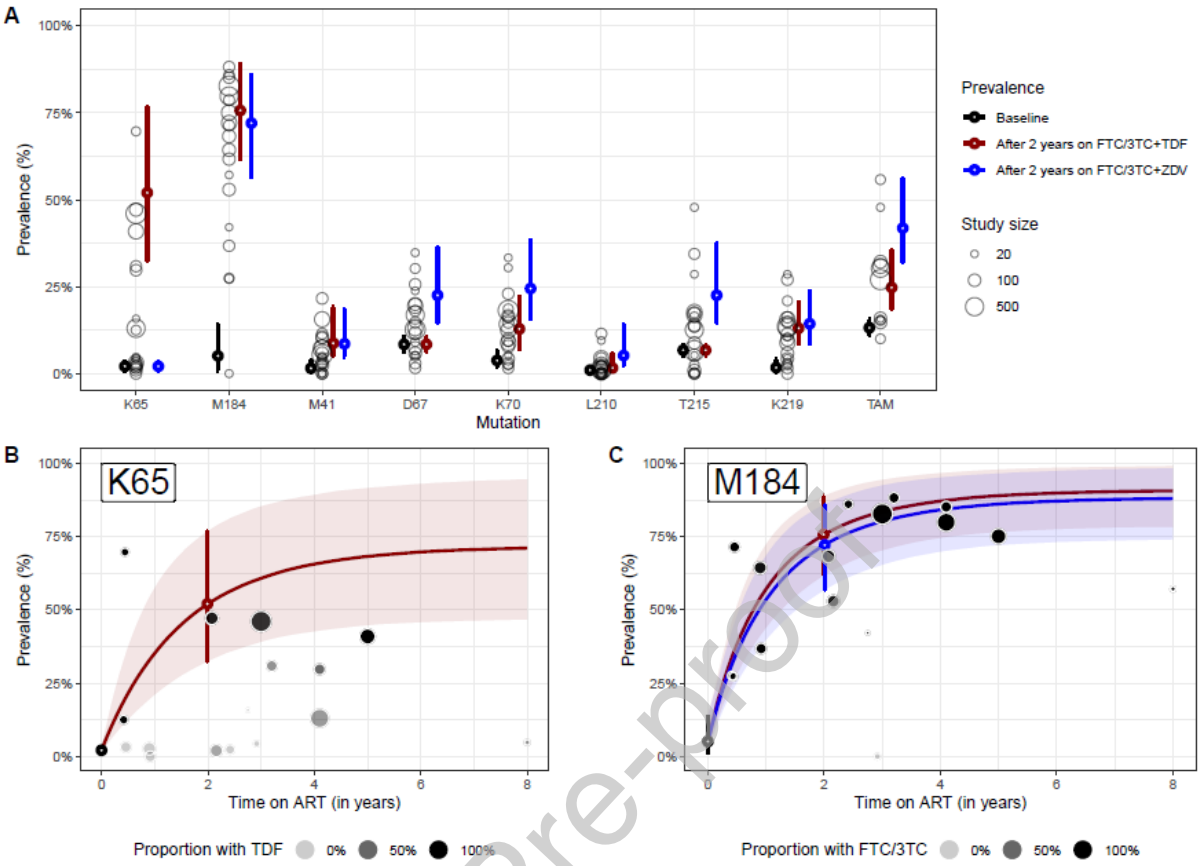

Fig. 4