Contents available at **PubMed**
**www.aidsreviews.com**

PERMANYER

Check for updates

**AIDS** Rev. 2023;25:136-144

# The impact of the M184V resistance mutation on treatment outcomes in patients with HIV infection: a systematic review and meta-analysis

*Mahmoud Kandeel*[1,2]

*[1]Department of Biomedical Sciences, College of Veterinary Medicine, King Faisal University, Al-Ahsa, Saudi Arabia; [2]Department of Pharmacology, Faculty of Veterinary Medicine, Kafrelsheikh University, Kafrelsheikh, Egypt*

## Abstract

***HIV is a global deliberating infectious disease. Of note, more than 36 million people living with HIV (PLHIV) with approximately newly diagnosed 1.5 million cases annually. M184V is a single base mutation in the highly conserved YMDD domain of reverse transcriptase (RT). It is one of the most encountered resistances associated with mutations to nucleoside RT inhibitors. There were continuous efforts to evaluate the impact of M184V mutation on the treatment outcomes in PLHIV. Therefore, the present systematic review was executed to reveal the virological failure, virological suppression, and resistance to antiretroviral therapy (ART) regimens in PLHIV with the M184V mutation. All clinical studies comparing the treatment outcomes among PLHIV harboring or not harboring M184V mutation were appropriate for systematic review and meta-analysis. The present systematic review included six articles, encompassing 4760 PLHIV. Of them, 1222 (25.67%) patients had M184V mutation, while 3538 (74.32%) PLHIV did not. The meta-analysis showed that patients with M184V mutation were 1.87 times more liable to virological failure (risk ratio [RR] 1.87; 95% 1.09, 3.20; p = 0.02). Furthermore, pooling the data from two studies revealed a significantly higher risk of viral blips (RR 2.26; 95% 1.47, 3.46; p = 0.0002). Concerning discontinuation of ART, there was no statistical difference between patients with and without M184V mutation (RR: 0.99; 95% 0.78, 1.25; p = 0.90). The present study revealed the negative impact of the M184V mutation on treatment outcomes in PLHIV. This included a higher risk of virological failure and viral blips, relative to patients without the mutation. Such patients may benefit from more aggressive and combined therapy for better disease management.***

## Keywords

***M184V mutation. Resistance. Antiretroviral therapy. Reverse transcriptase. Adherence. Viral blips.***

## Introduction

HIV is a global deliberating infectious disease. Of note, more than 36 million people living with HIV (PLHIV) with approximately newly diagnosed 1.5 million cases annually[1,2]. Since the introduction of antiretroviral therapy (ART), the clinical course of HIV has changed radically. The disease has become a manageable chronic condition with significantly reduced HIV-related mortality and morbidities. However, the issues of treatment toxicity,

**Correspondence to:**
Mahmoud Kandeel
E-mail: mkandeel@kfu.edu.sa

Received in original form: 24-02-2023
Accepted in final form: 05-09-2023
DOI: 10.24875/AIDSRev.23000002

adherence, and tolerability have been raised, particularly with increased life expectancy among PLHIV. The estimated genotypic resistance to combined ART is 5% after the 1st year. This figure rose to 10% after 2 years of ART, and approximately 30% of PLHIV developed virological failure within 6 years of ART. This highlighted the need to adjust the available ART to limit potential adverse events and drug interaction and achieve virological success[3-6].

The reverse transcriptase (RT) enzyme in HIV is multifunctional, posing RNA and DNA-dependent DNA polymerase activities. RT inhibitors' nucleoside and non-nucleoside analogs as terminators for nascent DNA synthesis. Being involved in different mechanisms, the RT enzyme is exceptionally prone to errors, resulting in mutations in the viral genome and subsequent drug resistance[7-9]. Of note, HIV-resistant variants can persist for an unknown duration in viral reservoirs and re-emerge, impacting the therapeutic response to the current ART[10].

M184V is a single base mutation in the highly conserved YMDD region of RT. It is one of the most encountered resistances associated with mutations to nucleoside RT inhibitors. This mutation could affect nearly 70% of the patients who failed to respond to first-line ART[11]. The pre-existed M184V mutation within the polymerase domain of the RT has unique effects on the response to different ART. Mutations near the RT enzymatic active site with M184V mutation may hinder the formation of competent polymerization complexes, reducing the therapeutic efficacy of ART. Paradoxically, the M184V mutation may decrease HIV fitness, increasing the susceptibility of HIV RT to zidovudine and tenofovir[12,13].

The development of drug resistance drastically contributes to ART failure in PLHIV. Treating such patients is often challenging, with more usage of combined ART and a more increase in drug-related toxicity. Identification of M184V mutation may impact the clinical decisions to implement combinations of ART in PLHIV[14]. Such knowledge is necessary to preserve the optimal therapeutic benefits by achieving the desired virological suppression. The current evidence showed controversial findings of the impact of M184V mutation on the outcomes of ART efficacy in PLHIV. There is an urgent clinical need to answer the efficacy of ART in patients harboring or not harboring M184V mutation[15].

There were continuous efforts to evaluate the impact of M184V mutation on the treatment outcomes in PLHIV. These efforts are scanty, raising clinicians' awareness to gather the related evidence in a comprehensive report[16]. Therefore, the present systematic review was executed to reveal the virological failure, virological suppression, and resistance to ART regimens in PLHIV with the M184V mutation. Integrating this knowledge in clinical practice will help to identify PLHIV at higher risk of virological failure. This will improve the results of ART by assorting PLHIV with the most beneficial therapy.

## Methods

This systematic review and meta-analysis were performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[17] and the Cochrane collaboration guidelines[18] (Supplementary Table 1). The methodology of the present systematic review was registered in the PROSPERO database (registration number; CRD42022381059).

### *Data source*

A systematic literature search was performed from the inception up to December 8th, 2022, using these databases: Google Scholar, PubMed, ISI, SIGLE, Scopus, Clinical trials, VHL, mRCT, NYAM, EMBASE, ICTRP, and Cochrane Collaboration. The search strategy used vocabulary terms specific to each searched database. The manual search was executed, screening the references of the included studies to reveal all extra articles that were not indexed. The following keywords were used; "M184V," "coronavirus," "human immunodeficiency virus," "HIV," "AIDS," and "acquired immunodeficiency syndrome."

### *Study selection*

All clinical studies comparing the treatment outcomes among PLHIV, receiving antiretroviral regimens, and harboring or not harboring M184V mutation were appropriate for systematic review and meta-analysis. Non-comparative studies, studies with inaccessible data, animal studies, guidelines, review articles, comments, case reports, letters, posters, book chapters, and editorials were excluded. The screening processes were performed independently to assess the eligibility of the revealed articles against the inclusion criteria. The screening processes were summarized using PRISMA flowchart.

### *Data extraction*

The characteristics data were revealed from the eligible studies. This included the study ID, year of publication, study region, study design, and study period. Baseline characteristics of the included articles were extracted, including sample size, patients' age, ethnicity, and gender. The data relating to HIV infection were extracted,

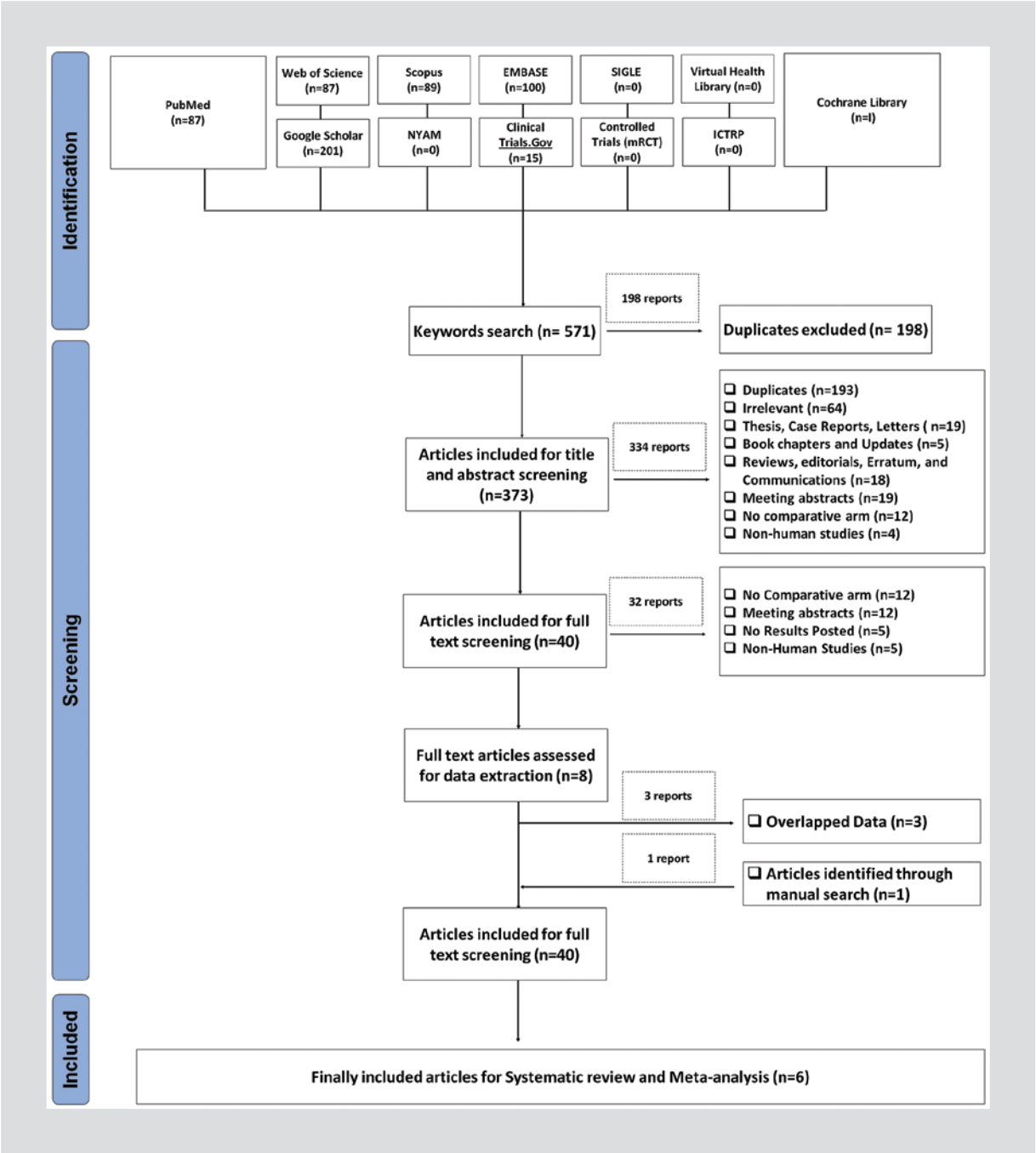


**Figure 1.** *PRISMA flow chart showing the process of the literature search, title, abstract, full-text screening, systematic review, and meta-analysis.*

consisting of the duration of viral suppression, CD4+ count (per $mm^3$), history of AIDS diagnosis, course of the disease, and treatment regimens. The data relating to M184V mutation, which included antiviral response, treatment class before and after switching, virological blips, and treatment discontinuation, were extracted. Two authors extracted the data blindly in Microsoft Excel sheet.

## *Quality assessment of the included studies*

The quality of the observational articles was evaluated using the National Institute of Health quality assessment tool[19]. The articles were categorized into bad, fair, or good when the score was > 30%, 30-65%, or < 65%, respectively.

**Table 1. Baseline demographic characteristics of the included studies**

| Study ID | | Study region | Study design | Study period | Sample size | | Age (years) | | Gender (male) | | Years from HIV diagnosis | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | M184V | Control | M184V | Control | M184V | | M184V | Control |
| | | | | | Number | Number | Mean ± SD | Mean ± SD | Number | Number | Mean ± SD | Mean ± SD |
| 1 | Chen et al., 2020[22] | Taiwan | Retrospective study | 1 September 2017 and 31 May 2019 | 100 | 400 | 40.3 ± 10.0 | 39.7 ± 9.2 | 98 | 392 | NR | NR |
| 2 | Gagliardini et al., 2018[23] | Italy | Retrospective study | NR | 87 | 349 | 52 (48-57) | 46 (39-53) | 53 | 257 | 19.2 (16.1-23.0) | 7.8 (3.8-13.7) |
| 3 | Gregson et al., 2020[24] | United kingdom | Retrospective study | NR | 817 | 628 | NR | NR | NR | NR | NR | NR |
| 4 | Olearo et al., 2019[25] | Italy | Observational longitudinal study | January 16, 2014 up To February 2018 | 137 | 1489 | 53.3 (51.6-55.0)* | 48.5 (47.9-49.0)* | 95 | 1170 | 20.2 (19.2-21.3)* | 10.6 (10.2-10.9)* |
| 5 | Rial-Crestelo et al., 2020[26] | Spain | Observational study | May 2018 to July 2020 | 21 | 20 | 53.4 (47.1-57.6) | 50.8 (42.9-55.3) | 16 | 16 | 21.5 (17.5-23.5) | 16.9 (12-27.4) |
| 6 | Santoro et al., 2022[27] | France, Italy, Spain | Observational study | NR | 60 | 652 | 56 (51-61) | 50 (42-58) | 37 | 511 | NR | NR |

| Study ID | | Study region | Study design | Study period | ART duration | | Treatment regimen | CD4 lymphocyte count (mm$^3$) | | | | Quality assessment | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | M184V | Control | | Baseline | | Nadir | | | |
| | | | | | Mean ± SD | Mean ± SD | | M184V | Control | M184V | Control | | |
| | | | | | | | | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | % | Decision |
| 1 | Chen et al., 2020[22] | Taiwan | Retrospective study | 1 September 2017 and 31 May 2019 | NR | NR | Elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide | 516 (403-687) | 583 (441-745) | NR | NR | 75% | Good |
| 2 | Gagliardini et al., 2018[23] | Italy | Retrospective study | NR | NR | NR | lamivudine -based DT | 632 (409-922) | 620 (453-780) | 147 (57-199) | 224 (81-313) | 75% | Good |

(Continues)

**Table 1. Baseline demographic characteristics of the included studies *(continued)***

| Study ID | | Study region | Study design | Study period | ART duration | | Treatment regimen | CD4 lymphocyte count (mm$^3$) | | | | Quality assessment | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | M184V | Control | | Baseline | | Nadir | | | |
| | | | | | Mean ± SD | Mean ± SD | | M184V | Control | M184V | Control | | |
| | | | | | | | | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | % | Decision |
| 3 | Gregson et al., 2020[24] | United kingdom | Retrospective study | NR | NR | NR | Tenofovir + Cytosine Analog + NNRTI | NR | NR | NR | NR | 66.66% | Good |
| 4 | Olearo et al., 2019[25] | Italy | Observational longitudinal study | January 16, 2014 up To February 2018 | NR | NR | Abacavir, Lamivudine, Dolutegravir | 665 (649-680)* | 667 (612-722)* | 178 (155-201)* | 232 (224-241)* | 75% | Good |
| 5 | Rial-Crestelo et al., 2020[26] | Spain | observational study | May 2018 to July 2020 | 18.8 (17.2-21) | 13.1 (7.9-21.6) | Lamivudine | NR | NR | NR | NR | 66.66% | Good |
| 6 | Santoro et al., 2022[27] | France, Italy, Spain | observational study | NR | NR | NR | DTG plus 3TC | 695 (481-885) | 682 (511-897) | NR | NR | 75% | Good |

ART: antiretroviral therapy; CD4: cluster of differentiation 4; DTG: dual therapy with dolutegravir; 3TC: plus lamivudine; NR: non-reported; SD: standard deviation; RTI: reverse transcriptase inhibitors. *Mean and 95% confidence interval.

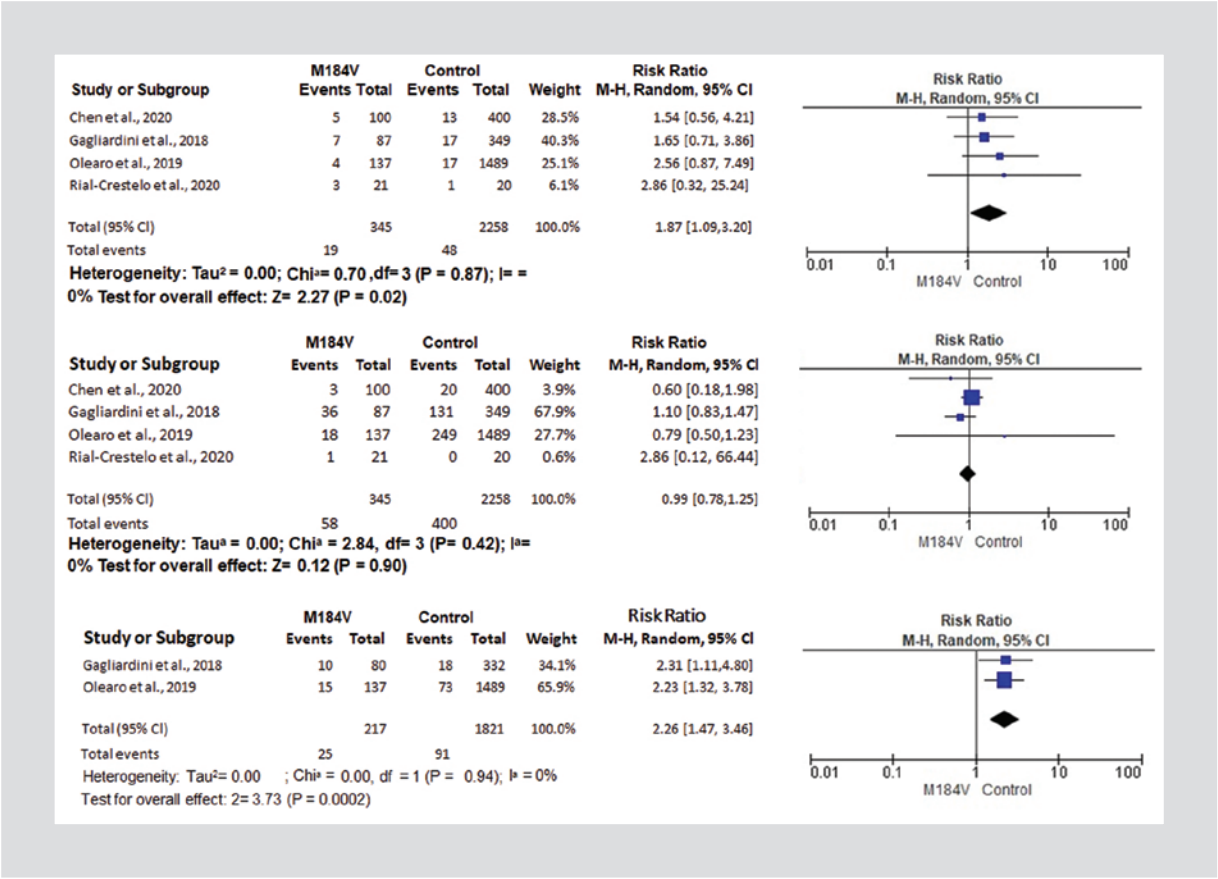


**Figure 2.** *Forest plot of summary analysis of the risk ratio and 95% confidence interval (CI) of the risk of (a) virological failure between patients with M184V and without the mutation, (b) discontinuation of treatment between patients with M184V and without the mutation, and (c) viral blips between patients with M184V and without the mutation. Size of the blue square is proportional to the statistical weight of each trial. The gray diamond represents the pooled point estimate. The positioning of both diamonds and squares (along with 95% CIs) beyond the vertical line (unit value) suggests a significant outcome (inverse variance).*

### *Statistical analysis*

The risk ratio (RR) with 95% confidence interval (CI) was implemented for pooling the dichotomous outcomes. The random-effects model was used when the heterogeneity between the eligible articles was revealed. Statistical heterogeneity was evaluated using Higgins $I^2$ statistic (> 50%), and the Cochrane Q (Chi-square test), at the value of $p < 0.10$[20]. Data analysis was performed using Review Manager version 5.4[21]. The difference was considered statistically significant when the probability value (p) < 0.05.

## Results

Searching the literature resulted in 571 articles. Consequently, 198 studies were excluded, yielding 373 studies suitable for screening. Out of them, 334 studies were ousted during the title and abstract screening processes. This resulted in 40 articles suitable for full-text screening. Among them, eight articles were eligible for data extraction, of which three were eliminated. One article was included in the manual search, yielding six studies for meta-analysis. The search approach for the included databases is revealed in Supplementary Table 2. The screening processes are shown in the PRISMA flowchart (Fig. 1).

### *Demographic characteristics of the eligible articles*

The present systematic review and meta-analysis included six articles[22-27], encompassing 4760 PLHIV. Of them, 1222 (25.67%) patients had M184V mutation, while 3538 (74.32%) PLHIV did not. There were 299 males in the M184V group, in contrast to 2346 within the control group. The average age of the included patients ranged from 40.3 to 56 years among the M184V

group and from 39.7 to 50.8 years among the control group. The baseline CD4+ lymphocyte count ranged from 516 to 695, while the nadir levels ranged from 147 to 178 and from 224 to 232 among the M184V and the control groups, respectively. All the included studies included patients taking antiretroviral drugs. All the included articles were of good quality (Table 1).

## *Study outcomes*

### Virological failure

Four articles, including 2603 PLHIV, assessed the risk of virological failure among patients with M184V and without[22,23,25,26]. Virological failure was established among 19 (5.5%) patients with M184V mutation, in contrast to 48 (2.1%) patients without the mutation. In the random-effects model ($I^2$ = 0%, p = 0.87), the meta-analysis showed that patients with M184V mutation were 1.87 times more liable to virological failure (RR: 1.87; 95% 1.09, 3.20; p = 0.02), in comparison to patients without M184V mutation (Fig. 2a).

### Discontinuation of treatment

The risk of treatment discontinuation between patients with M184V mutation and without was assessed within four articles, including 2603 cases[22,23,25,26]. Discontinuation of the treatment was revealed among 58 (16.81%) patients with M184V mutation and 400 (17.7%) patients without the mutation. In the random-effects model ($I^2$ = 0%, p = 0.42), there was no statistical difference between patients with and without M184V mutation (RR 0.99; 95% 0.78, 1.25; p = 0.90) (Fig. 2b).

### Viral blips

Two articles included 2038[23,25] patients who reported the impact of M184V mutation on the risk of viral blips. Of the included patients with M184V mutation, 25 developed viral blips (9.22%). Pooling the data in the random-effects model ($I^2$ = 0%, p = 0.94) revealed a significantly higher risk of viral blips among patients with M184V mutation (RR 2.26; 95% 1.47, 3.46; p = 0.0002) (Fig. 2c).

## Discussion

The M184V mutation is a prevalent resistant-associated mutation in PLHIV. It was presented in nearly 25% of samples in ART-treated patients who developed virological failure[28]. The emergence of HIV drug resistance is inevitable and necessitates continuous research to improve the current practice. The available literature is inconclusive to generate enough evidence regarding the impact of M184V mutation on the treatment efficacy in PLHIV. This is because of insufficient randomized clinical trials, the relatively small sample size of the published studies, and the short follow-up periods. Therefore, this meta-analysis was performed to address the impact of M184V mutation resistance on the virological failure, discontinuation of treatment, and viral blips in PLHIV. The present study revealed a significantly higher risk of virological failure and viral blips among PLHIV and had M184V mutation resistance. There was a similar risk of treatment discontinuation between patients harboring and those non-harboring the M184V mutation. M184V mutation was associated with a higher risk of losing virological control in virologically suppressed PLHIV. The use of additional drugs may be beneficial in the settings of ART drug resistance.

In the present study, the M184V mutation increased the risk of virological failure. Similarly, Hauser et al., 2022 reported that the M184V mutation was the most encountered mutation among patients with virological failure 2 years after ART[29]. M184V mutation impedes the compensatory mutagenesis of HIV, decreasing the formation of the reverse transcription initiation complex. Particularly, M184V mutation affects the integration with tRNA primer, explaining the late appearance of the pause product at +3 position in the reactions carried out by the muted RT. This affects the synergistic fashion of the initiation reaction, resulting in significant impairment in the synthesis of (-)ss DNA[13].

M184V mutation may be found in the HIV reservoirs for a prolonged time. Prolonged viral suppression with ART might dilute the quasispecies harboring the M184V in the viral reservoir. The duration and level of viral replication are associated with the persistence of M184V mutation. The size of the reservoir progressively declines during the first 3-4 years of suppression and tends to be plateaued after that[30]. The seeding of the HIV reservoirs with proviruses carrying the mutation led to persistent resistance to ART over time. Lamivudine is an integrated part of all recommended antiretroviral regimens in both first- and second-line ART. M184V mutation is commonly presented in patients with virological failure and on lamivudine and emtricitabine therapy[31,32]. Conversely, the presence of M184V mutation might confer some advantages, reducing the viral fitness and the replication capacity of HIV and increasing the susceptibility of HIV to tenofovir[33,34].

Preexisting M184V mutation was frequently detected in patients with suppressed HIV. It was associated with

other resistance mutations, longer ART duration, and baseline CD4+ cell count[35]. In the present study, patients with M184V mutation have more than two folds increase in the risk of viral blips. This confirms the negative impact of M184V mutation on maintaining viral suppression. The burden of M184V mutation supports the need for routine viral load testing for early detection of virological failure and a timely switch to more beneficial therapeutic options[36]. Switching to more effective therapy improves adherence and avoids toxicity in PLHIV under ART. Switching to dual and triple therapies may be effective for maintaining viral suppression in PLHIV and having M184V mutation. However, detecting the most effective treatment in patients harboring M184V mutation deserved further evaluation[37,38].

Of note, Gagliardini et al., 2018, reported a negative impact of coinfection with the hepatitis B virus on the virological response and durability of antiretroviral regimens. The presence of HBsAg limits the use of lamivudine-containing DT and regimens without tenofovir. Furthermore, coinfection with HBV was reported to increase the risk of M184V mutation even without previous exposure to ART. However, the data on the impact of coinfection with HBV in patients with HIV and M184 mutations are limited, requiring further investigations[32,40].

The present systematic review revealed the impact of M184V mutation on the treatment outcomes in PLHIV. Paradoxically, the present study's findings had some limitations and need some caution while interpreting it. All the eligible articles were observational, conferring a relative risk of bias. Furthermore, the adherence-related data to ART were not reported thoroughly, which may confound the treatment outcomes. There was considerable heterogeneity between the eligible articles. This may reveal the difference in treatment regimens, duration of HIV suppression, time since diagnosis of HIV, demographic characteristics of the included patients, study design, and follow-up periods. The presence of the M184V mutation warrants further research to tackle the limitations of the current systematic review and to optimize a treatment protocol for patients with existing M184V mutation.

## Conclusions

The present systematic review revealed the negative impact of the M184V mutation on treatment outcomes in PLHIV. This included a higher risk of virological failure and viral blips, relative to patients without the mutation. There was no impact of the M184V mutation on treatment discontinuation. Further randomized controlled trials with considerable sample sizes and long-term follow-up periods are required to alleviate the limitations of the current systematic review study.

## Supplementary data

Supplementary data are available at DOI: 10.24875/AIDSRev.23000002. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

## Acknowledgments

The authors extend their appreciation to the Deanship of Scientific Research, Vice Presidency for Graduate Studies and Scientific Research, King Faisal University, Saudi Arabia (Project# AN00055). The author would like to thank Yasmin ELrefaey and Dr. Mohamed Aly for their help during data extraction and inspection.

## Funding

This work was supported through the Annual Funding track by the Deanship of Scientific Research, Vice Presidency for Graduate Studies and Scientific Research, King Faisal University, Saudi Arabia [Project No. AN00055].

## Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that no patient data appear in this article.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

**Use of artificial intelligence for generating text.** The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

## References


1. Nematova N, Almatova U, Khonimkulova RK, Khasanova F. Epidemiological situation in hiv-infections and prevention. In: Materials of International Science Practice Conference; 2022. p. 67.
2. UNIAIDS. Preliminary UNAIDS 2021 Epidemiological Estimates. Geneva: Uniaids; 2021.
3. Palella FJ Jr., Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr. 2006;43:27-34.
4. Samji H, Cescon A, Hogg RS, Modur SP, Althoff KN, Buchacz K, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. PLoS One. 2013;8:e81355.
5. Lohse N, Obel N. Update of survival for persons with HIV infection in Denmark. Ann Intern Med. 2016;165:749-50.
6. Gupta R, Hill A, Sawyer AW, Pillay D. Emergence of drug resistance in HIV Type 1-infected patients after receipt of first-line highly active antiretroviral therapy: a systematic review of clinical trials. Clin Infect Dis. 2008;47:712-22.
7. Liu X. The categories, mechanisms and features of nonnucleoside reverse transcriptase inhibitors of HIV-1. Highl Sci Eng Technol. 2023;36:1193-201.
8. Wang Y, De Clercq E, Li G. Current and emerging non-nucleoside reverse transcriptase inhibitors (NNRTIs) for HIV-1 treatment. Expert Opin Drug Metab Toxicol. 2019;15:813-29.
9. Günthard HF, Calvez V, Paredes R, Pillay D, Shafer RW, Wensing AM, et al. Human immunodeficiency virus drug resistance: 2018 recommendations of the international antiviral society-USA panel. Clin Infect Dis. 2019;68:177-87.
10. Cilento ME, Kirby KA, Sarafianos SG. Avoiding drug resistance in HIV reverse transcriptase. Chem Rev. 2021;121:3271-96.
11. Santoro MM, Sabin C, Forbici F, Bansi L, Dunn D, Fearnhill E, et al. Drug-resistance development differs between HIV-1-infected patients failing first-line antiretroviral therapy containing nonnucleoside reverse transcriptase inhibitors with and without thymidine analogues. HIV Med. 2013;14:571-7.
12. Ross L, Parkin N, Chappey C, Fisher R, Clair MS, Bates M, et al. Phenotypic impact of HIV reverse transcriptase M184I/V mutations in combination with single thymidine analog mutations on nucleoside reverse transcriptase inhibitor resistance. AIDS. 2004;18:1691-6.
13. Wei X, Liang C, Götte M, Wainberg MA. Negative effect of the M184V mutation in HIV-1 reverse transcriptase on initiation of viral DNA synthesis. Virol. 2003;311:202-12.
14. Wainburg MA. The impact of the M184V substitution on drug resistance and viral fitness. Expert Rev Anti-Infect Ther. 2004;2:147-51.
15. Bandera A, Gori A, Clerici M, Sironi M. Phylogenies in ART: HIV reservoirs, HIV latency and drug resistance. Curr Opin Pharmacol. 2019;48:24-32.
16. McCluskey SM, Siedner MJ, Marconi VC. Management of virologic failure and HIV drug resistance. Infect Dis Clin North Am. 2019;33:707-42.
17. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
18. Collaboration C. Cochrane Handbook for Systematic Reviews of Interventions. London: Cochrane Collaboration; 2008.
19. National Heart, Lung, and Blood Institute. National Institute of Health, Quality Assessment Tool for Observational Cohort and Cross-sectional Studies. Bethesda: National Heart, Lung, and Blood Institute; 2014.
20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60.
21. Collaboration C. Review Manager (RevMan) [Computer Program]. Version 5.4. London, UK: The Cochrane Collaboration; 2020.
22. Chen GJ, Lee YL, Lee CH, Sun HY, Cheng CY, Tsai HC, et al. Impact of archived M184V/I mutation on the effectiveness of switch to co-formulated elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide among virally suppressed people living with HIV. J Antimicrob Chemother. 2020;75:2986-93.
23. Gagliardini R, Ciccullo A, Borghetti A, Maggiolo F, Bartolozzi D, Borghi V, et al. Impact of the M184V resistance mutation on virological efficacy and durability of lamivudine-based dual antiretroviral regimens as maintenance therapy in individuals with suppressed HIV-1 RNA: a cohort study. Open forum Infect Dis. 2018;5:ofy113.
24. Gregson J, Rhee S, Datir R, Pillay D, Perno C, Derache A, et al. Human immunodeficiency virus-1 viral load is elevated in individuals with reverse-transcriptase mutation M184V/I during virological failure of first-line antiretroviral therapy and is associated with compensatory mutation L74I. J Infect Dis. 2020;222:1108-16.
25. Olearo F, Nguyen H, Bonnet F, Yerly S, Wandeler G, Stoeckle M, et al. Impact of the M184V/I mutation on the efficacy of abacavir/lamivudine/dolutegravir therapy in HIV treatment-experienced patients. Open Forum Infect Dis. 2019;6:ofz330.
26. Rial-Crestelo D, de Miguel R, Montejano R, Dominguez-Dominguez L, Aranguren-Rivas P, Esteban-Cantos A, et al. Long-term efficacy of dolutegravir plus lamivudine for maintenance of HIV viral suppression in adults with and without historical resistance to lamivudine: week 96 results of ART-PRO pilot study. J Antimicrob Chemother. 2021;76:738-42.
27. Santoro MM, Armenia D, Teyssou E, Santos JR, Charpentier C, Lambert-Niclot S, et al. Virological efficacy of switch to DTG plus 3TC in a retrospective observational cohort of suppressed HIV-1 patients with or without past M184V: the LAMRES study. J Global Antimicrob Resist. 2022;31:52-62.
28. Assoumou L, Charpentier C, Recordon-Pinson P, Grudé M, Pallier C, Morand-Joubert L, et al. Prevalence of HIV-1 drug resistance in treated patients with viral load >50 copies/mL: a 2014 French nationwide study. J Antimicrob Chemothe. 2017;72:1769-73.
29. Hauser A, Goldstein F, Reichmuth ML, Kouyos RD, Wandeler G, Egger M, et al. Acquired HIV drug resistance mutations on first-line antiretroviral therapy in Southern Africa: systematic review and Bayesian evidence synthesis. J Clin Epidemiol. 2022;148:135-45.
30. Besson GJ, Lalama CM, Bosch RJ, Gandhi RT, Bedison MA, Aga E, et al. HIV-1 DNA decay dynamics in blood during more than a decade of suppressive antiretroviral therapy. Clin Infect Dis. 2014;59:1312-21.
31. Palich R, Teyssou E, Sayon S, Abdi B, Soulie C, Cuzin L, et al. Kinetics of archived M184V mutation in treatment-experienced virally suppressed HIV-infected patients. J Infect Dis. 2022;225:502-9.
32. Verhofstede C, Noë A, Demecheleer E, De Cabooter N, Van Wanzeele F, Van Der Gucht B, et al. Drug-resistant variants that evolve during non-suppressive therapy persist in HIV-1-infected peripheral blood mononuclear cells after long-term highly active antiretroviral therapy. J Acquir Immune Defic Syndr. 2004;35:473-83.
33. Castagna A, Danise A, Menzo S, Galli L, Gianotti N, Carini E, et al. Lamivudine monotherapy in HIV-1-infected patients harbouring a lamivudine-resistant virus: a randomized pilot study (E-184V study). Aids. 2006;20:795-803.
34. Margot NA, Johnson A, Miller MD, Callebaut C. Characterization of HIV-1 resistance to tenofovir alafenamide *in vitro*. Antimicrob Agents Chemother. 2015;59:5917-24.
35. Sax PE, Andreatta K, Molina JM, Daar ES, Hagins D, Acosta R, et al. High efficacy of switching to bictegravir/emtricitabine/tenofovir alafenamide in people with suppressed HIV and preexisting M184V/I. AIDS. 2022;36:1511-20.
36. Trotter AB, Hong SY, Srikantiah P, Abeyewickreme I, Bertagnolio S, Jordan MR. Systematic review of HIV drug resistance in the World Health Organization Southeast Asia region. AIDS Rev. 2013;15:162.
37. Pisaturo M, Onorato L, Russo A, Martini S, Chiodini P, Signoriello S, et al. Risk of failure in dual therapy versus triple therapy in naïve HIV patients: a systematic review and meta-analysis. Clin Microbiol Infect. 2021;27:28-35.
38. Baldin G, Ciccullo A, Borghetti A, Di Giambenedetto S. Virological efficacy of dual therapy with lamivudine and dolutegravir in HIV-1-infected virologically suppressed patients: long-term data from clinical practice. J Antimicrob Chemother. 2019;74:1461-3.
39. Jain MK, Zoellner CL. Entecavir can select for M184V of HIV-1: a case of an HIV/hepatitis B (HBV) naive patient treated for chronic HBV. AIDS. 2007;21:2365-6.