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Review

Treatment Management Challenges in Naïve and Experienced HIV-1-Infected Individuals Carrying the M184V Mutation

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Abstract: M184V is a single-base mutation in the YMDD domain of reverse transcriptase (RT). The M184V resistance-associated mutation is related to virological unresponsiveness to lamivudine (3TC) and emtricitabine (FTC) and induces high-level resistance to these two antiretroviral agents. M184V is rapidly selected in the setting of non-suppressive antiretroviral therapy (ART) and accumulates in the HIV reservoir. There were continuous efforts to evaluate the impact of M184V mutation on the treatment outcomes in people with HIV (PWH). Since lamivudine remains an extensively used part of recommended antiretroviral combinations, M184V is commonly detected in patients with virological failure. ART guidelines do not recommend the use of drugs impacted by resistance-associated mutations as they have been confirmed to comprise a risk factor for virological failure. However, previous authors suggest that 3TC/FTC can remain active even in the presence of M184V. Obtaining the viral resistance profile for each individual both treated or ART-naïve is a key challenge for lifelong treatment management.Given the potential benefits of lamivudine in the ART combinations, the investigation of M184V remains of high interest for clinicians and researchers. This is a review of literature for the challenges in treating both naïve and experienced individuals carrying the M184V resistance mutation, including virological failure, virological suppression, and resistance to ART.

Keywords: HIV-1; drug resistance; M184V; mutation; naïve; experienced

1. Introduction

The HIV epidemic remains a major public health concern and treating people with HIV (PWH) is accompanied by significant challenges despite current efficacious antiretroviral therapy (ART). The emergence of drug resistance due to the selection and/or transmission of HIV-1 variants harboring resistance-associated mutations (RAMs) is strongly correlated to high rates of virological failure (VF) in either ART-naïve or ART-experienced patients [1]. This phenomenon compromises the success of commonly used potent antiretroviral drugs. One of the most frequently encountered RAMs is the M184V mutation in the reverse transcriptase (RT) region of *pol* gene which confers high-level resistance to lamivudine (3TC) and emtricitabine (FTC) and potentially leads to VF in PWH being treated with regimens containing these antiretroviral agents, resulting in limited number of available treatment options [2-8]. Therefore, genotypic resistance testing is extremely important prior to initiation or modification of ART, in order to obtain a viral resistance profile that can be used to guide appropriate treatment decisions [9]. In case of demonstrated RAMs current ART guidelines recommend against the use of drugs with documented resistance while choosing a regimen containing at least two, preferably three, fully active drugs. Nevertheless, several experts suggest that continuation of treatment with 3TC or FTC might be beneficial despite presence of the M184V mutation [9].

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2. Evolution of Antiretroviral Therapy

Over the past few decades, the landscape of antiretroviral therapy has evolved dramatically, resulting in significant alteration of the natural course of the HIV-1 infection, which is currently considered a manageable chronic condition [10]. Initially, treatment regimens consisted of monotherapy with nucleoside reverse transcriptase inhibitors (NRTIs) such as zidovudine or dual therapy with NRTIs. However, these approaches were abandoned due to rapid development of resistance and poor treatment outcomes [11].

The widespread use of combination ART (cART) revolutionized HIV treatment by introducing regimens containing various classes of antiretroviral drugs, which targeted at different stages of the HIV-1 replication cycle, thereby reducing the likelihood of resistance while increasing the rates of virologic suppression. Recommended cART regimens are based on a backbone, consisting of two NRTIs, usually combined with a third agent from another class, such as a protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitor (NNRTI) or integrase strand transfer inhibitor (INSTI) [9,11].

In recent years, a shift towards simpler and more potent regimens has been noted, facilitated by the development of newer antiretroviral drugs demonstrating more favorable resistance and tolerability profiles. Single-tablet regimens containing multiple drugs have become increasingly popular due to the apparent reduced pill burden, allowing for convenience and improved adherence [11,12].

Despite these groundbreaking advancements, several challenges remain in managing HIV infection, particularly in populations with limited access to healthcare resources and those impacted by high rates of treatment failure or drug resistance [4,6,13]. Addressing these challenges by developing novel therapies, optimizing treatment strategies, and improving access to care for all PWH is central to ongoing research efforts.

3. Epidemiology of M184V Mutation

The epidemiology of the M184V mutation is directly related to the dynamics of HIV-1 drug resistance, primarily affecting individuals with a history of ART exposure. Drug resistance often emerges in ART-experienced individuals due to selection pressure exerted by administered antiretroviral agents, enhancing the replication of mutated HIV-1 variants. This leads to increased viral load and eventual virological failure, contributing to acquired drug resistance. Subsequently, these mutations can be transmitted to newly infected individuals who have not yet received ART, resulting in transmitted drug resistance [1]. According to a systematic review that investigated the prevalence of pretreatment and acquired HIV-1 mutations associated with drug resistance, the estimated global prevalence of acquired RAMs was 58% for any NRTIs, mainly at position M184, whereas the prevalence of pretreatment NRTI-associated mutations was significantly lower (4%), with M184V/I being among the most frequent (1%) [2].

Influenced by factors such as treatment availability, adherence patterns, and the local prevalence of drug-resistant strains, the prevalence of the M184V mutation varies geographically as was previously shown by studies conducted in diverse regions, highlighting the significant prevalence of NRTI-associated mutations, with M184V emerging as a key mutation. A French study found that the most commonly detected NRTI RAMs were M184V/I with an estimated prevalence of 25.9% [3]. In Cameroon, NRTI-associated mutations were detected in 30% of ART-experienced individuals and 2.4% of ART-naïve individuals, with M184V being the most common mutation observed [4]. Similar findings were reported in a meta-analysis conducted in China, demonstrating high rates of M184V in both ART-treated and ART-naïve individuals [5]. Furthermore, studies in South Africa and India have underscored the widespread prevalence of NRTI-associated resistance mutations, with M184V being notably prevalent [6,7]. These mutations result in significant clinical management challenges and contribute to virological failure, complicating the treatment of people with HIV and potentially facilitating the transmission of drug resistance [1,8]. Surveillance efforts and molecular epidemiological studies are essential for monitoring trends in drug resistance mutations and designing public health strategies to mitigate their impact on HIV treatment outcomes.

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4. Clinical Impact of M184V Mutation

The M184V mutation represents one of the most clinically significant mutations in the context of HIV-1 infection and antiretroviral therapy. It is located in the reverse transcriptase gene of the HIV-1 virus and induces high-level resistance to certain NRTIs, particularly lamivudine (3TC) and emtricitabine (FTC), whereas it increases susceptibility of the virus to tenofovir [8,14].

The clinical impact of the M184V mutation is multifaceted and has implications for both treatment-naive and treatment-experienced individuals. Acknowledging its significance is extremely important for guiding treatment decisions and optimizing therapeutic outcomes.

In treatment-naive patients, the presence of the M184V mutation can influence the selection of initial ART regimens [9]. Since M184V confers resistance to 3TC and FTC, which are commonly included in first-line regimens due to their efficacy and tolerability, the presence of this mutation may limit the choice of NRTIs [8]. This highlights the importance of baseline resistance testing to identify individuals with pre-existing resistance mutations, including M184V, and tailor treatment accordingly [7,9,13,14].

Furthermore, in treatment-experienced individuals, the emergence of the M184V mutation complicates the management of virological failure and selection of salvage therapy. Reduced susceptibility to 3TC and FTC conferred by M184V may compromise the efficacy of these agents in subsequent treatment regimens. This necessitates the use of alternative NRTIs or other drug classes with preserved activity against M184V-resistant virus [9].

Moreover, the M184V mutation can impact the overall fitness of the virus and its replicative capacity. While M184V confers resistance to specific NRTIs, it may also result in reduced viral replication capacity and fitness, which could influence the trajectory of disease progression and the likelihood of treatment success. However, the clinical implications of these fitness costs require further investigation and may vary depending on the specific viral genetic background and host factors [1,8,14].

Additionally, the selection pressure exerted by NRTIs, particularly 3TC and FTC, may favor the emergence of additional resistance mutations, leading to multidrug resistance and further limiting treatment options [13,14].

5. Challenges in Naïve Patients

Detecting the M184V mutation in treatment-naive individuals poses initial challenges due to cost constraints or local guidelines, potentially leading to suboptimal treatment outcomes. Limited treatment options arise from resistance to key antiretroviral components like lamivudine and emtricitabine, complicating regimen selection. Despite limited direct resistance to other drugs, such as tenofovir and abacavir, the presence of M184V can impede virological response to therapy, emphasizing the need for vigilant monitoring and early intervention in cases of virological failure [7].

The presence of M184V in ART-naïve patients not only restricts current treatment options but also raises the risk of cross-resistance to other antiretroviral agents [4,7]. The selection pressure from M184V and other mutations may prompt multidrug resistance, constraining future therapeutic choices. Therefore, proactive detection of M184V and strategic management are crucial to prevent treatment failure and preserve future treatment avenues [7,14].

Recent research sheds light on the influence of the M184V mutation on viral load during virological failure on first-line ART and its prevalence in patients experiencing virological failure on first-line NNRTI-based ART, particularly in Southern Africa.

One study delves into how the M184V/I mutation impacts viral load in individuals failing first-line ART containing 3TC or FTC, tenofovir disoproxil fumarate (TDF) and an NNRTI and found that those with the M184V/I mutation had higher HIV viral loads. Despite resistance to 3TC and FTC conferred by M184V/I, individuals with this mutation exhibited similar viral loads to those without it. Compensatory mutations, like L74I, were associated with increased replication efficiency of M184V/I-harboring viruses, possibly explaining these unexpected findings [14].

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Complementing this study, a systematic review focusing on PWH in Southern Africa experiencing virological failure on first-line NNRTI-based ART found high levels of the M184V/I mutation after two years, especially when combined with tenofovir or zidovudine. The prevalence of NRTI/NNRTI drug resistance mutations underscores the common occurrence of resistance in this population, influencing treatment decisions and the efficacy of second-line regimens. Despite NRTI resistance, dolutegravir-based regimens may remain effective, as evidenced by studies where NRTI resistance did not hinder virological response to second-line regimens [13].

These findings highlight the intricate relationship between drug resistance mutations, viral replication capacity, and treatment outcomes in individuals failing first-line ART, particularly in regions with high prevalence of drug resistance such as Southern Africa. Understanding resistance patterns is crucial for refining treatment strategies and transitioning to dolutegravir-based first-line ART in resource-limited settings [13].

Therefore, routine resistance testing before initiating antiretroviral therapy is highly recommended, particularly in settings with high HIV prevalence or known drug-resistant strains. This testing aids in identifying baseline mutations, including M184V, and guides regimen selection. However, challenges like access, cost, and infrastructure hinder widespread testing, necessitating innovative solutions and collaborative efforts among clinicians, researchers, and policymakers to ensure timely diagnosis, access to effective therapies, and comprehensive patient support [6].

6. Challenges in Experienced Patients

Treatment-experienced patients face unique challenges in managing HIV infection, particularly when harboring the M184V mutation. These individuals usually have been exposed to multiple antiretroviral drugs over time, thus increasing the likelihood of accumulation of resistance mutations and further complicating the selection of salvage therapy.

Selecting an effective salvage therapy regimen in experienced patients with the M184V mutation requires careful consideration of the individual's treatment history, resistance profile, comorbidities, and treatment preferences. Alternative NRTIs with activity against M184V-resistant virus, such as tenofovir disoproxil fumarate (TDF) or abacavir (ABC), may be considered [9].

In some cases, experienced patients with the M184V mutation may require a switch to alternative antiretroviral regimens due to virological failure, toxicity, or treatment intolerance. Switch strategies should take into account the patient's resistance profile, previous treatment history and the availability of alternative agents with activity against M184V-resistant virus. Close monitoring of treatment response and virological outcomes is essential following regimen switches to ensure adequate viral suppression and prevent further development of drug resistance [9,12,15].

One significant challenge that arises when managing virally suppressed individuals prior to regimen switch is the inability to perform RNA-based drug resistance testing due to very low viral load, which does not allow for adequate amplification of viral plasma RNA. This can be overcome by alternatively performing proviral DNA genotyping; a method using cellular HIV DNA derived from peripheral blood mononuclear cells (PBMCs) in order to obtain a comprehensive genotypic resistance profile [10].

A study investigating the behavior of drug-resistant viral variants (DRVs) harboring the M184V mutation in the proviral DNA of virally suppressed patients demonstrated that the persistence of the M184V mutation was associated with the duration and level of HIV-RNA replication under 3TC/FTC therapy. While the mutation decreased over time in HIV-DNA, it was more frequently persistent in patients with longer past replication under 3TC/FTC. The study highlighted the importance of detecting DRVs for predicting virological failure and underscored the need for careful consideration when recycling drugs with viral activity potentially impaired by past resistance in ART management [16].

According to a recent publication, consensus was reached among virologists and clinicians who agreed using the Delphi method that a regimen containing a second-generation INSTI plus 3TC or FTC plus one NRTI confers low risk of VF in a virally suppressed patient for at least one year carrying the M184V substitution documented on the current DNA genotype and/or on an RNA genotype

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performed within the last 5 years. However, when examining the combination of a second-generation INSTI plus 3TC or FTC, under the same conditions, virologists expressed a strong concern about significant VF risk over time, whereas clinicians did not reach a consensus [10].

Recent studies and a comprehensive review investigate the efficacy of switching to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in maintaining virologic suppression among HIV-1 patients, including those with archived antiretroviral resistance, such as M184V/I mutations.

Particularly, one study examined the efficacy of switching to B/F/TAF in maintaining HIV-1 RNA suppression among participants with archived antiretroviral resistance. Surprisingly high rates of pre-existing resistance substitutions, notably M184V/I mutations, were found among suppressed participants who switched to B/F/TAF. Despite this, high rates of virological suppression were maintained for up to 48 weeks with no development of resistance to study drugs. This study emphasized the importance of comprehensive resistance testing prior to treatment initiation or regimen switch, concluding that switching to B/F/TAF was noninferior to other regimens [15].

Another study specifically investigated the efficacy of switching to B/F/TAF in Black Americans with HIV-1. Results showed that only few participants experienced HIV RNA levels of 50 copies/mL or higher through week 48 after switching to B/F/TAF, indicating a high rate of virologic suppression. Notably, participants with pre-existing resistance to NRTIs, including M184V/I mutation, achieved high rates of virologic suppression upon switching, with no development of treatment-emergent resistance during the study period. This study highlighted the real-world efficacy of B/F/TAF in maintaining virologic suppression, even in the presence of pre-existing NRTI resistance [17].

Furthermore, a review presented recent literature supporting the use of B/F/TAF for consolidating therapy and maintaining virologic suppression, especially in individuals with M184V/I mutations based on randomized trials that demonstrated the efficacy of B/F/TAF in maintaining virologic suppression, even in participants with pre-existing M184V/I mutations. The review underscored the importance of medication adherence for sustaining virologic suppression on B/F/TAF [18].

These results are further supported by in vitro data, according to which viral strains carrying the M184V substitution exhibit diminished viral strength and heightened susceptibility to tenofovir. Thus, persisting to an emtricitabine/tenofovir-based therapy in cases involving the M184V mutation aims to uphold selective pressure, favoring a less robust virus that is particularly susceptible to tenofovir [8,15].

Moreover, another potential treatment option for experienced individuals harboring the M184V mutation is the abacavir/lamivudine/dolutegravir (ABC/3TC/DTG) regimen as was demonstrated by a study that investigated the influence of the M184V/I mutation on virological outcomes in virally suppressed HIV-1 patients switching to ABC/3TC/DTG. Results indicated that patients with a documented M184V/I mutation tended to have a lower CD4 nadir and a longer history of antiviral therapy. Despite these differences, there was no significant association between the presence of M184V and the incidence of virological failure (VF). These findings suggest that the abacavir/lamivudine/dolutegravir regimen effectively maintains virological suppression in treatment-experienced patients, regardless of M184V/I mutation status. The study highlights the potential of this regimen as a viable treatment option for individuals with a history of antiretroviral therapy and documented M184V/I mutation. However, the authors emphasize the need for further research to validate these results over an extended follow-up period and explore any potential long-term impacts on treatment efficacy [19].

Additionally, one study explored the efficacy of switching to dolutegravir plus lamivudine (DTG + 3TC) in maintaining HIV viral suppression among aviremic individuals with historical resistance to lamivudine. At week 48, 92.7% of participants maintained virologic suppression with HIV-1 RNA levels fewer than 50 copies/mL, and no cases of virologic failure were reported. Participants with historical lamivudine resistance or detection of lamivudine resistance mutations achieved resuppression on DTG + 3TC, challenging the assumption that DTG + 3TC functions as dolutegravir monotherapy in patients with prior history of lamivudine resistance. This suggests that

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lamivudine may provide significant antiviral activity to dolutegravir despite the presence of archived lamivudine resistance mutations, underscoring the potential of DTG + 3TC as a reduced-drug regimen for maintenance of HIV suppression in integrase inhibitor-naïve individuals with historical lamivudine resistance, with careful assessment of baseline resistance mutations recommended [20].

Similarly, a meta-analysis investigated the impact of the M184V/I mutation on virologic response to DTG + 3TC in populations with suppressed HIV-1. Minimal impact of prior M184V/I mutations on virologic suppression was demonstrated after switching to DTG + 3TC, suggesting that 3TC-containing regimens, such as DTG + 3TC, can remain effective in individuals with historical M184V/I mutations, with low virologic failure rates and no emergent integrase strand transfer inhibitor resistance reported. This indicates that M184V/I mutations may have minimal impact on the effectiveness of DTG + 3TC as a switch strategy in virologically suppressed individuals with incomplete treatment histories, but further data are needed to explore the impact of various factors [21].

In summary, these results provide evidence supporting the efficacy of DTG + 3TC in maintaining HIV viral suppression, even in individuals with historical resistance to lamivudine, and suggest that the presence of M184V/I mutations may have minimal impact on the effectiveness of this regimen [20-22].

Despite significant advances in research regarding efficacy of specific combinations of antiretroviral agents, equal emphasis should be placed on adherence of individuals carrying the M184V mutation to antiretroviral therapy to achieve and sustain virological suppression [4,9,12,18]. Regular monitoring of adherence, using methods like self-reporting and pill counts could be a useful tool for the prevention of virological failure and transmission of resistance due to poor patient adherence, while monitoring of viral load and CD4 cell count aids in assessing treatment response, promptly detecting virological rebound and guiding clinical decision-making [9,12].

7. Conclusions and Future Directions

The literature reviewed highlights the complexity of treatment management challenges faced by both naive and experienced HIV-1 infected individuals carrying the M184V mutation [22]. For naive patients, the emergence of transmitted drug resistance, particularly the prevalence of M184V mutation, poses significant hurdles in achieving successful virological suppression with first-line ART [7,13,14,22]. Understanding the epidemiology of these mutations, especially in regions with high rates of drug resistance, is crucial for optimizing treatment strategies and transitioning to more effective regimens, such as dolutegravir-based therapy, in resource-limited settings [6,13,22].

For experienced patients, recent studies have shown that the efficacy of switching to newer antiretroviral regimens, such as bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF), abacavir/lamivudine/dolutegravir (ABC/3TC/DTG) or dolutegravir plus lamivudine (DTG + 3TC), offers promising avenues for maintaining viral suppression despite historical resistance mutations, including M184V/I. These studies also underscore the importance of comprehensive resistance testing prior to treatment initiation or regimen switch to inform personalized therapeutic approaches. Moreover, ongoing research into the kinetics of archived M184V mutations in long-term virally suppressed patients provides answers regarding the persistence of resistance-associated mutations and their impact on treatment outcomes over time [10,15-22].

Looking ahead, future directions in HIV treatment management should prioritize strategies that address the expanding landscape of drug resistance, including the development of novel antiretroviral agents with improved resistance profiles. Additionally, efforts to enhance adherence to treatment regimens, monitor virological outcomes, and optimize therapeutic interventions tailored to individual patient needs are paramount. Collaborative efforts between clinicians, researchers, and public health officials are essential for advancing our understanding of the challenges posed by M184V mutation and implementing evidence-based interventions to improve clinical outcomes and reduce the transmission of drug-resistant HIV strains [12].

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