Effectiveness of Dolutegravir + Lamivudine in Real-world Studies in People with HIV-1 With M184V/I Mutations: A Systematic Review and Meta-analysis

Madhusudan Kirby, Tristan J. Barber, Clotilde Allavena, Anne-Genevieve Marcelin, Simona Di Giambenedetto, Juan Pasqua, Nicola Gigante, Mary Wempe, Cale Harrison, Tammy Wynne, and Julie Priest

Introduction

• M184V/I is the most common RAM selected by 3TC.
• Clinical development phase 3 RCTs excluded participants with known or suspected RAMs.
• The presence of archived M184V/I mutations in phase 3 trials evaluating switch to DTG/3TC (TANGO, n=4; SALSA, n=3) did not impair virologic efficacy.
• Absence of historical resistance results or availability of prior genotype (poorly TANGO/SALSA analysis, n=294) also had no impact on results.

• In clinical practice, prior history of resistance is not always available when considering treatment options.
• Real-world evidence (RWE) can help address the knowledge gap of whether switching to DTG + 3TC is safe in real-world clinical practice when full treatment history or historical genotype results are not available.

• This meta-analysis describes VF at Weeks 24, 48, and 96 using real-world data from RWE studies reporting DTG + 3TC in a suppressed switch setting, with historical RNA- or archived proviral DNA-detected M184V/I.

• A sensitivity analysis was performed using RCT data.

Methods

• A systematic literature review was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Figure 1A).
• Embase®, Ovid MEDLINE®, Ovid In-Process, and Cochrane Library (January 2013-March 2020) and relevant conference abstracts (2016-2020) were searched for real-world studies reporting virologic outcomes for PWH receiving DTG + 3TC.
• The target literature review was performed to identify RCTs assessing M184V/I impact on DTG + 3TC therapy efficacy (Figure 1B).
• Studies were screened for suppressed switch populations reporting M184V/I mutations before DTG + 3TC therapy initiation.

• The primary objective was to evaluate switching to DTG + 3TC with M184V/I-affected populations more generally to the overall population of interest.
• Common-effects (or fixed-effects) models assumed that the included studies are the population and are more informative when zero VF events are observed.

• For the secondary objective, analyses were performed using RCT data.

• In both RWE and RCT data sets, base analyses were performed using identical VF definitions; sensitivity analyses were performed using all studies regardless of VF definition to maximize sample size.

Results

Table 1. Summary of VF Definition and with M184V/I RAMs Receiving DTG + 3TC in Studies and RCTs

<table>
<thead>
<tr>
<th>Study (cohort)</th>
<th>Proportion of with pre-existing M184V/I</th>
<th>M184V/I identification method</th>
<th>time-point, week</th>
<th>VF outcomes, n (%)</th>
<th>VF definition</th>
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</thead>
<tbody>
<tr>
<td>RWE studies</td>
<td></td>
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<tr>
<td>Hidalgo et al.</td>
<td>15/66 (23.07%)</td>
<td>Prevalent RNA and proviral DNA</td>
<td>24</td>
<td>2/23 confirmed VL &lt;40 c/mL</td>
<td>3TC (n=174)</td>
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<tr>
<td>(Dartmouth)</td>
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<tr>
<td>Saini et al.</td>
<td>2/150 (1.33%)</td>
<td>Prevalent RNA and proviral DNA</td>
<td>24</td>
<td>2/23 confirmed VL &lt;40 c/mL</td>
<td>3TC (n=174)</td>
</tr>
<tr>
<td>(LAWRES)</td>
<td></td>
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<tr>
<td>Natarajan et al.</td>
<td>20/365 (5.50%)</td>
<td>Prevalent RNA and proviral DNA</td>
<td>24</td>
<td>2/23 confirmed VL &lt;40 c/mL</td>
<td>3TC (n=174)</td>
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<tr>
<td>(TANGO)</td>
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<tr>
<td>Benfield et al.</td>
<td>48/695 (6.76%)</td>
<td>Prevalent RNA and proviral DNA</td>
<td>24</td>
<td>2/23 confirmed VL &lt;40 c/mL</td>
<td>3TC (n=174)</td>
</tr>
<tr>
<td>(COCASAFE)</td>
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<tr>
<td>Galal et al.</td>
<td>7/175 (4.06%)</td>
<td>Prevalent RNA and proviral DNA</td>
<td>24</td>
<td>2/23 confirmed VL &lt;40 c/mL</td>
<td>3TC (n=174)</td>
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<tr>
<td>(NAT)</td>
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<tr>
<td>Hidalgo-Torresi</td>
<td>4/178 (2.30%)</td>
<td>Prevalent RNA and proviral DNA</td>
<td>24</td>
<td>2/23 confirmed VL &lt;40 c/mL</td>
<td>3TC (n=174)</td>
</tr>
<tr>
<td>SOLAM-19</td>
<td>14 (25.00)</td>
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| RCTs           |                                        |                              |                 |                   |               |
| DOLLAM-10      | 17 (100%)                              | Prevalent RNA and proviral DNA | 24              | 2/17 confirmed VL <40 c/mL | 3TC (n=174)   |
| ART PRO        | 17 (100%)                              | Prevalent RNA and proviral DNA | 24              | 2/17 confirmed VL <40 c/mL | 3TC (n=174)   |
| SOLAM-12       | 10 (100%)                              | Prevalent RNA and proviral DNA | 24              | 2/10 confirmed VL <40 c/mL | 3TC (n=174)   |
| SOLAM-13       | 17 (100%)                              | Prevalent RNA and proviral DNA | 24              | 2/17 confirmed VL <40 c/mL | 3TC (n=174)   |
| ART PRO        | 17 (100%)                              | Prevalent RNA and proviral DNA | 24              | 2/17 confirmed VL <40 c/mL | 3TC (n=174)   |
| SOLAM-14       | 10 (100%)                              | Prevalent RNA and proviral DNA | 24              | 2/10 confirmed VL <40 c/mL | 3TC (n=174)   |
| SOLAM-15       | 17 (100%)                              | Prevalent RNA and proviral DNA | 24              | 2/17 confirmed VL <40 c/mL | 3TC (n=174)   |

**VF Estimates**

• Random-effects models are associated with greater uncertainty vs common-effects models but can be used to estimate results for the wider population of interest based on the sample studies used in the analysis.

• Common-effects (or fixed-effects) models assume the included populations are the population of interest and can be more appropriate and informative when zero VF events are observed.

• RWE common-effects models estimated the proportions (95% CI) of individuals with VF at Week 24: 0.01 (0.00-0.03) and Week 48: 0.02 (0.00-0.05). For Week 48: RCT common-effects models estimated the proportions (95% CI) of individuals with VF were 0.01 (0.00-0.05) at Week 48; the random-effects estimate for this time point is in Figure 2B.

• Common-effects models better represent the Week 24 and Week 96 data consisting of zero observed events each (Figure 2B); random-effects models estimated Week 24 and Week 96 proportions were 0.00 (0.00-0.00).

Conclusions

• Overall, pre-switch M184V/I prevalence was low in PWH in RWE studies.
• Real-world studies of PWH with historical or archived M184V/I receiving DTG + 3TC identified low incidence of VF through 96 weeks and no reported cases of INSTI treatment-emergent mutations; these findings were consistent with results from RCTs.

• Genotypic data at the time of VF were unavailable and the occurrence of resistance mutations to 3TC or DTG at failure could not be described.

• This meta-analysis provides reassuring data on outcomes with DTG + 3TC in PWH with incomplete history or in cases where M184V/I was inadvertently missed.

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Preparation Author: Julie Priest. juli.e.priest@viivhealthcare.com