Dolutegravir-Based Regimens Viral Load Decay at Week 4 Could Predict Sustained Viral Suppression at Week 96

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Introduction
● The medium- and long-term implications of rapid viral load early-phase decay during integrase inhibitor–based therapy are not fully understood
● The integrase inhibitor dolutegravir (DTG) plus 2 nucleoside reverse transcriptase inhibitors has been evaluated in 3 phase III studies in treatment-naive subjects
● DTG-based regimens (DBRs) achieved non-inferiority in SPRING-2 vs raltegravir (RAL)–based regimens, while superiority was shown in SINGLE and FLAMINGO vs Atripla® and boosted darunavir (DRV/r)–based regimens, respectively1-3
● This analysis was conducted to assess the predictive value of rapid virological response (RVR) at Week 4 on sustained virological response (SVR) at Week 96 in naive subjects treated with DBRs

Methods
● Post hoc cross-sectional analysis of subjects enrolled in the naive DTG phase III clinical trials, SPRING-2, SINGLE, and FLAMINGO
● RVR and SVR were assessed at Weeks 4 and 96, respectively, based on HIV-1 RNA <50 as determined by FDA snapshot
● Positive (PPV) and negative predictive values (NPV) predictive values were calculated: PPV as the proportion of subjects suppressed at Week 4 who were also suppressed at Week 96, and NPV as the proportion of subjects not suppressed at Week 4 who were also not suppressed at Week 96

Results

Table 1. PPV and NPV of SVR at Week 96

<table>
<thead>
<tr>
<th>SVR at Week 96</th>
<th>SINGLE</th>
<th>SPRING-2</th>
<th>FLAMINGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG (N=414)</td>
<td>80</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>EFV (N=419)</td>
<td>84</td>
<td>85</td>
<td>82</td>
</tr>
<tr>
<td>DTG (N=411)</td>
<td>78</td>
<td>82</td>
<td>76</td>
</tr>
<tr>
<td>RAL (N=242)</td>
<td>82</td>
<td>85</td>
<td>74</td>
</tr>
<tr>
<td>DRV/r (N=242)</td>
<td>85</td>
<td>85</td>
<td>77</td>
</tr>
</tbody>
</table>

PPV (%), 95% CI:
- SINGLE: DTG (80% [74, 85]), EFV (84% [78, 90]), RAL (82% [76, 88]), DRV/r (85% [77, 91])
- SPRING-2: DTG (85% [80, 90]), EFV (85% [82, 90]), RAL (85% [80, 90]), DRV/r (85% [80, 90])
- FLAMINGO: DTG (82% [74, 90]), EFV (85% [80, 90]), RAL (82% [76, 88]), DRV/r (85% [77, 91])

NPV (%), 95% CI:
- SINGLE: DTG (25% [14, 36]), EFV (28% [19, 37]), RAL (32% [21, 43]), DRV/r (26% [14, 38])
- SPRING-2: DTG (28% [19, 37]), EFV (30% [21, 42]), RAL (32% [21, 43]), DRV/r (26% [14, 38])
- FLAMINGO: DTG (28% [19, 37]), EFV (30% [21, 42]), RAL (32% [21, 43]), DRV/r (26% [14, 38])

A total of 2139 subjects were analysed, including those receiving DBRs and comparator arms; 1067 subjects received DTG across the 3 studies

The analysis revealed that 70% of subjects receiving DBRs achieved RVR at Week 4, and 80% attained SVR at Week 96. The PPV and NPV of SVR in the DBR study population were 85% (95% CI: 82%-87%) and 29% (95% CI: 24%-34%), respectively (Figure 1)

The PPV of the DBRs was numerically higher than for efavirenz (EFV) or DRV/r plus 2 nucleosides and similar to that with RAL plus 2 nucleosides (Table 1 and Figure 1)

The NPV with RAL was numerically higher than with DBRs, reflecting that more DBR subjects without RVR ended with SVR

Discussion
● Limitations of this analysis included using a post-randomisation measure (Week 4 virological response) as a predictor, and the inclusion of an open-label randomised clinical trial, where there was potential for bias
● The PPVs for DBRs were consistent with or numerically higher than the comparators, correlating with study outcomes at Week 96, which supports the predictive value of undetectability at Week 4

Figure 1. PPV and NPV Associated With All DBR Regimens and Individual Studies

Conclusions
● This analysis suggests that RVR at Week 4 with DBRs is a potential predictor of SVR at Week 96
● The NPV of RVR with DTG is numerically lower than with RAL
● Characterisation of patients who do not achieve RVR and subsequent undetectability deserves further investigation
● These data may support clinicians to further individualise therapy and monitoring

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