Switching to maraviroc in combination with 2 NRTIs: Experience at a large London teaching hospital

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Background

- The use of maraviroc 300mg BD with 2 NRTIs is non-inferior compared to efavirenz in the MERIT-ES study, but a higher rate of virologic failure was noted in the CCR5-arm
- Maraviroc has relatively few toxicities and may present a useful switch option in patients with CCR5-tropic HIV-1
- The use of genotypic viral tropism assays to determine HIV co-receptor tropism using PBMCs for patients with undetectable HIV RNA viral load (VL) could allow use of the CCR5 receptor antagonist maraviroc (MVC) in a switch strategy
- We looked at the indications for switch and short term outcomes of using maraviroc in combination with 2 NRTIs as a switch strategy within our large London HIV cohort

Methods

- Patients switching to maraviroc in combination with 2 NRTIs between 2008 and 2012 were identified using our HIV database
- Treatment history and indication for switch were identified using the database and notes based search
- Virological outcomes were assessed for those with more than 24 weeks follow up post switch (or failure)
- Patients prescribed MVC+2NRTIs as their first ART regimen were excluded from this analysis, results stated as number (percentage), or median [range]

Results (1)

- 28 patients were switched to maraviroc in combination with 2 N(t)RTIs

Table 1: Baseline characteristics

Parameter	Total
Demographics	
Age	45 [30, 65]
Male	22 (78)
Ethnicity	
White	19 (68)
Black/Black African	7 (25)
Other	2 (7)
Risk	
MSM	20 (71.4)
Heterosexual	7 (25)
Blood products	1 (3.6)
IVDU	0 (0)
HIV history	
Number years on ART	6.1 [0.4, 21]
Nadir CD4	243 [40, 747]
N prior ART regimens	3 [1, 15]
Prior virological failure	7 (25)
Prior exposure to	
PI/r	21 (75)
NNRTI	19 (67.8)
INI	0 (0)
Resistance prior to switch	
Nil confirmed	26 (93)
NRTI	
Confirmed	2 (7.1)
Suspect	1 (3.6)
NNRTI	
Confirmed	0 (0)
Suspected	3 (10.7)
PI	1 (3.6)
Prior failure NRTI-based ART	7 (25)
At switch	
VL<50c/mL	23 (82)
CD4 (cells/mm^3)	721 [176, 1223]
Tropism (genotypic)	
CCR5	26 (92.8)
Mixed/dual	1 (3.6)
Unable to amplify	1 (3.6)

Results (2)

Table 2: Indication for switch to MVC + 2NRTIs

Indication for switch	N (%)
Dyslipidaemia	**8 (28.5)**
PI/r related	6 (21.4)
Other cause	2 (7.1)
CNS disturbances	**5 (17.8)**
Efavirenz related	3 (10.7)
Non-Efavirenz ART related	2 (7.1)
GI disturbances	**4 (13.2)**
PI/r related	3 (10.7)
Other cause	1 (3.6)
Other	**11 (39.3)**
Lipodystrophy	2 (7.1)
Other ART toxicity	
Darunavir transaminitis	1 (3.6)
Atazanavir renal stone	1 (3.6)
Patient choice	1 (3.6)
Other	4 (13.2)
Not stated	2 (7.2)

- 68% (19/28) indications for switch were related to ART toxicity, including CNS disturbances with saquinavir/r (1), atazanavir/r (1) (table 2)
- Other indications include a PI-sparing regimen to avoid interactions with long term corticosteroids (1), and switching to MVC to improve CNS penetration in patient with neuropsychiatric deficient (1), and use for a patient with Kaposi's sarcoma due to potential role on KS angiogenesis

Table 3: Antiretroviral combinations prior to switch

Prior Combination	N (%)
HAART	**26 (92.9)**
PI/r + 2NRTI	17 (61)
NNRTI+NRTI	7 (25)
uPI + 2NRTI	2 (7.1)
Dual therapy	**1 (3.6)**
DRV/r/MVC	1 (3.6)
PI/r monotherapy	**1 (3.6)**
DRV/r 800/100mg OD	1 (3.6)

Table 4: 2 NRTI + MVC combinations used

Combinations at switch	N (%)
TDF + FTC + MVC 300mg BD	19 (67.9)
TDF + 3TC + MVC 300mg BD	2 (7.1)
ABC + 3TC + MVC 300mg BD	6 (21.4)
TDF + ABC + MVC 300mg BD	1 (3.6)

- One patient requested to be switched to maraviroc 600mg once daily after 12 weeks on regimen, and maintained VL<50c/ml at 24 and 48 weeks

Table 5: Outcomes of switch to regimen

Outcomes	Total
Follow up on regimen	
<24 wks	4 (16.7)
Not yet reached time point	3
Discontinued before time point	1
24-47 wks	24 (85.7)
Not yet reached time point	3
Discontinue prior to time point	1
Discontinued during time point	1
≥48 wks	18 (64)
Not yet reached time point	8
Discontinue prior to time point	2
Discontinue after time point	4
Virological FU for those remaining on Therapy, wks	56 [0, 113]
VL outcomes*	
VL<50c/ml (24wk)[a]	20/25 (80)
VL<50c/mL (48wk)[a]	15/20 (75)
Any viral failure[b]	7 (25%)
CD4 change	
24 wks, cells/mm^3	+41 [-411, 520]
48 wks , cells/mm^3	+91 [-380, 679]

a – VL<50c/ml (time point) = (number on regimen with VL<50c/mL) / (total with VL FU + discontinuations by time point)
b - Viral failure defined as ≥2xVL>50c/ml >4wks apart or any VL>400c/mL

Results (3)

- One patient with VL<50c/ml at switch had intermittent viraemia but VL<50c/ml at 24 and 48 weeks. Patient subsequently found to have archived M184V, T215Y and L210W mutations which failed to re-emerge on repeat genotypes during viraemia on ABC/3TC/MVC. Repeat genotypic tropism demonstrated CCR5-tropic virus

Tropism determination:

- 93% (26/28) had genotypic tropisms determined on PBMCs, 24/26 with samples with VL<50c/mL, and 2 on samples with VL of 65c/ml and 434c/mL
- One patient with D/M tropic virus at switch maintained VL<50c/ml on regimen at last FU at 47 wks
- 8 patients with baseline CCR5-tropic virus had FU tropism testing, all remaining CCR5-tropic with mean duration FU 13 (6, 24) months

Table 6: Indications for discontinuation of regimen

Discontinued regimen	**6 (21.4)**
Median time till discontinue regimen, wks	57 [20, 69]
Reason for discontinuation	
Viral failure	2 (7.1)
Poor adherence with viral failure	4 (14.2)
On discontinuation switch to:	
2NRTI+MVC+PI/r	3 (10.7)
Stop all ART	3 (10.7)

- Of those who discontinued the regimen (table 6), none had prior detectable resistance mutations, although 66% (4/6) had failed on previous ART regimen, compared to 13.6% (3/22) of those continuing therapy

Discussion

- Those who switched were predominantly virologically suppressed with good CD4 count experiencing ART related toxicities
- Discontinuation was predominantly related to poor adherence, with 50% (3/6) of those who discontinued the regimen having detectable VL at switch to MVC+2NRTI, and subsequently stopping ART
- Interpretation of virological efficacy of regimen was limited by retrospective nature of study looking at follow up in clinical practice which is dependent on both patient history and clinician

Limitations

- Retrospective, medical notes-based audit
- Small numbers of patients.
- Relatively short duration of VL/CD4 follow up at inconsistent time points

Conclusions

- A switch strategy to maraviroc in combination with 2 NRTIs may be feasible for CCR5 tropic patients with undetectable VL without archived resistance.
- Viral failure was generally associated with poor adherence
- Formal switch studies are needed to assess this strategy in larger populations

References

- Heera J et al. MERIT-ES 96 week. IAS 2009, Abstract TUAB103