Efficacy of Integrase Inhibitor and Protease Inhibitor-based Three Drug Regimens in the Presence of the M184V/I Mutation: A Review of the Literature

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INTRODUCTION

- Drug resistance: important consideration in HIV therapy
- M184V/I: common mutation selected by 3TC and FTC[1]
- Can confer hypersusceptibility to AZT, d4T, and TFV and modest reduction in susceptibility to ABC and ddI[2]
- Has been common practice to maintain 3TC/FTC despite presence of M184V/I mutation, due to:
  - Safety, tolerability, convenience, residual partial virologic activity, beneficial effect on susceptibility
- Limited guidance pertaining to management of pts with M184V/I
- DHHS guidelines recommend switch options for individuals with virologic failure on first ARV regimen[3]:
  - bPI + 2 NRTIs or DTG + 1-2 active NRTIs or bPI + INSTI
- Current standard of practice is 3-drug regimen, however, patients with M184V/I on 3TC/FTC essentially only have 2 active drugs

OBJECTIVES

- To summarize available evidence regarding the efficacy (virologic suppression/failure) of 3-drug regimens including a bPI or INSTI + one active NRTI + 3TC/FTC in individuals with the M184V/I mutation

METHODS

- Literature review
- Databases: PubMed, EMBASE, Google scholar
- Recent HIV conference abstracts and posters
- Reference lists of identified studies were then searched for additional relevant literature

Search terms:

- ”M184V AND HIV or human immunodeficiency virus AND antiretroviral or ART or HAART or ARV”

Inclusion:

- 3 drug ARV regimens (excluding cobicistat/ritonavir booster) with specific mention of M184V in adults with HIV
- Date range: 1946 - September 2019

Exclusion:

- 1, 2, or 4 drug regimens, low barrier regimens (NNRTI-based, RAL-based), animal studies, PK studies, in-vitro studies, non-English studies

LEGEND

3TC: lamivudine
ABC: abacavir
ART: antiretroviral treatment
ARV: antiretroviral
ATV: atazanavir
AZT: zidovudine
BIC: bictegravir
bPI: boosted protease inhibitor
c/mL: copies/mL
d4T: stavudine
ddI: didanosine
DRV/r: darunavir/ritonavir
DTG: dolutegravir
EFV: efavirenz
ETV: etravirine
EVG/c: elvitegravir/cobicistat
f/u: follow-up
fAPV: fosamprenavir
FTC: emtricitabine
HAART: highly active antiretroviral therapy
GART: genotypic antiretroviral resistance testing
INSTI: integrase strand transfer inhibitor
IQR: interquartile range
LPV: lopinavir
NNRTI: non-nucleoside reverse transcriptase inhibitor
NRTI: nucleos(t)ide reverse transcriptase inhibitor
NVP: nevirapine
PI: protease inhibitor
PK: pharmacokinetic
RAL: raltegravir
RPV: rilpivirine
SQV: saquinavir
TAF: tenofovir alafenamide
TAM: thymidine analogue mutation
TDF: tenofovir disoproxil fumarate
TFV: tenofovir
VF: virologic failure
VL: viral load

RESULTS

Table 1. Summary of Literature on ARVs and the M184V/I mutation

Study Patients (n) Study Design	ARV status & Previous regimen	Patient Population	ART Used	Virologic Suppression at Baseline	Outcome Measured	Results & Median Duration of Therapy
Boosted PIs						
Hull (2009)[4] **n=184** **M184V: n=117** **Retrospective**	Treatment experienced Switched from: -NNRTI-based: n=56/117 (48%) -bPI-based: n=26/117 (22%) -Other: n=35/117 (30%)	117 pts had documented M184V & resistance to 3TC +/- NNRTI Excluded pts with additional NRTI/NNRTI/PI mutations	-Reg A: bPI + NRTI + 3TC/FTC (n=48) -Reg B: bPI + NRTI + 3TC/FTC + ≥1 additional agent (n=25) -Reg C: bPI + 2 NRTI +/- additional agent (3TC-sparing) (n=44)	VL <100,000 c/mL: -Reg A: 71% -Reg B: 60% -Reg C: 66%	Association between subsequent regimen and time to virologic suppression (2 consecutive VL <50 c/mL) after detection of M184V	Suppressed within study period: -Reg A: 71% -Reg B: 80% -Reg C: 73% No difference between regimens in VL suppression rates after M184V mutation (p=0.4434) 10.9 months (IQR 5.9-19.7)
Sahloff (2019)[5] **n=32** **M184V: n=32** **Retrospective**	Treatment experienced Switched from: -Not mentioned	32 pts had M184V/I per previous genotype/ phenotype: -M184V/I only: n=4/32 (13%) -M184V/I as only NRTI mutation: n=15/32 (47%)	DRV/r + TDF/FTC	VL <40 c/mL: n=4/32 (13%) VL <100,000 c/mL: n=23/32 (72%)	Virologic suppression (defined as VL <200 c/mL) VF defined as failure to achieve VL <200 c/mL or change in ART with VL >200 c/mL within 24 months of starting therapy	-Achieved VL <200 c/mL: n=27/32 (84%) -Achieved VL <40 c/mL: n=22/32 (69%) -VF: n=6/32 (19%) 21 months (range 6-24)
INSTIs						
Bictegravir						
Andreatta (2019)[6] **n=570** **M184V/I: n=54** **Post-hoc analysis of prospective studies**	Treatment experienced Switched from: -2 NRTI + bPI (DRV or ATV): n=289/570 (51%) -DTG/ABC/3TC: n=281/570 (49%)	54 patients had M184V/I Pre-existing resistance via historical genotype or proviral DNA obtained for n=543/570 (95%) Excluded pts with underlying resistance or previous VF	BIC/TAF/FTC	VL <50 c/mL for ≥3-6 months: n=570/570 (100%)	Proportion of pts with VL <50 c/mL at last on-treatment visit through wk 48 -Pts on BIC/TAF/FTC with M184V/I vs. pts without	Virologic suppression: -With M184V/I: n=52/54 (96%) -Without M184V/I: n=482/489 (99%) -Overall: n=561/570 (98%) No difference between all populations (p>0.05) 48 wks (end of trial)
Dolutegravir						
Olearo (2018)[7] **n=1626** **M184V: n=137** **Prospective observational**	Treatment experienced Switched from: -Not mentioned	Pts with archived M184V/I mutation: -At least 2 TAMs: n=58/137 (42%) -At least 3 TAMs: n=40/137 (30%)	DTG/ABC/3TC	VL ≤50 c/mL: n=137/137 (100%)	First VF (defined as 2 consecutive VL >50 c/mL or 1 VL >50 c/mL accompanied with ART change)	VF in pts: -With M184V/I n=4/137 (3%) vs. without M184V/I n=17/1489 (1%) (p=0.78) Time to f/u (median): with M184V/I = 312 days (IQR 176-510), without M184V/I = 285 days (IQR 153-435) (p=0.0186)
Elvitegravir						
Perez (2018)[8] **n=37** **M184V: n=37** **Prospective open-label single arm**	Treatment experienced Switched from: -FTC/TDF (54%) or ABC/3TC (46%) And, -3rd agent: NNRT (11%), PI (54%), INSTI (32%)	37 pts had M184V and/or M184I on historical genotype 16 pts had M184V/I detected by proviral DNA: -M184V/I only: n=8/37 (22%) -M184V/I + NNRTI-R: n=8/37 (22%)	EVG/c/TAF/FTC	VL <50 c/mL: n=37/37 (100%) -For ≥6 months	Absence of VL >50 c/mL on 2 consecutive visits or premature discontinuation with last available VL >50 c/mL	VL <50 copies/mL: n=37/37 (100%) 24 wks (outcome reported at trial midpoint)
Andreatta (2018)[9] **n=24** **M184V: n=5** **Retrospective**	Treatment experienced Switched from: -NNRTI (EFV, NVP, RPV, ETV) + FTC/TDF Or -PI/r (ATV, DRV, LPV, fAPV, SQV) + FTC/TDF	M184V detected by: -Historical: n=3/24 (13%) -Proviral only: n=2/24 (8%)	EVG/c/TDF/FTC	VL <50 c/mL: n=24/24 (100%) -For ≥6 months	VL at last study visit	VL <50 c/mL at wk 96: -Proviral M184V: n=2/2 (100%) -Historical M184V: n=1/3 (33%) 2/3 (66%) pts with historical M184V dropped out early with VL >50 c/mL (at wk 4 and 24) 100% suppressed in those who made it to 96 wks (n=3)
bPIs vs. INSTIs						
Sorstedt (2018)[10] **n=244** **M184V: unclear** **Retrospective**	Treatment experienced Switched from: -Not mentioned	Total NRTI resistance mutations recorded: -DTG: n=260 -PI/r: n=343 M184V (most common NRTI mutation): -DTG: n=95/260 (37%) -PI/r: n=95/343 (28%)	DTG + (ABC/3TC 59%, TFV/FTC 34%, other 7%) Or, PI/r (ATV, DRV, LPV) + (ABC/3TC 34%, TFV/FTC 50%, other 16%)	VL <50 c/mL: -PI/r: n=108/122 (88.5%) -DTG: n=91/122 (74.6%)	VF defined as increase of VL >200 c/mL for pts already suppressed with VL <50 c/mL	VF in pts: -DTG 4/122 (3%) vs. PI/r 3/122 (2%) Presence of baseline M184V in participants with VF: -DTG: n=2/4 (50%) -PI/r: n=3/3 (100%) DTG: 78 wks (IQR 50-98) PI/r: 75 wks (IQR 50-101)
Aboud (2019)[11] **n=627** **M184V: n=513** **Prospective**	Treatment experienced Switched from: -NNRTI: EFV (78%), NVP (22%) -NRTI: 3TC (70%), TDF (58%), FTC (29%), AZT (29%), ABC (9%)	M184V/I only: -DTG: n=77/312 (25%) -LPV/r: n=85/312 (27%) M184V/I with any other major NRTI mutation: -DTG: n=184/312 (59%) -LPV/r: n=167/312 (54%)	DTG or LPV/r + NRTI background (≥1 fully active agent): -AZT + 3TC -TDF + 3TC/FTC -TDF + AZT -ABC + 3TC	VL <400 c/mL: -DTG: n=11/312 (4%) -LPV/r: n=9/312 (3%)	Proportion of pts achieving viral suppression (defined as VL <50 c/mL) at wk 48	Viral suppression: -DTG: n=261/312 (84%) vs. LPV/r: n=219/312 (70%) -Non-inferiority achieved -Superiority achieved (p<0.0001) 48 wks (time of outcome report)
Various INSTIs						
Pronier (2017)[12] **n=75** **M184V: n=23** **Retrospective**	Treatment experienced Switched from: -2NRTI + 1 NNRTI: 35% -2 NRTI + 1 PI/r: 36% -2 NRTI + 1 INSTI: 17% -Other: 12%	23 pts with M184V on historical genotype: -184V alone or <2 TAMs: n=9 -184V & 65R: n=4 -184V & 74I/V: n=1 -184V & ≥2 TAMs: n=5 -184V & 74I/V & ≥2 TAMs: n=4	EVG/c/TFV/FTC (n=38) Or DTG/ABC/3TC (n=37)	VL <50 c/mL: 100% -At baseline	Proportion of participants with VF (defined as 2 consecutive VL >50 c/mL)	1/75 (1%) had VF -Pt had poor adherence, prior VF, no prior exposure to INSTI, M184V mutation 13 months (range 1-84)
Demarest (2018)[13] **n=715** **M184V: n=25** **Retrospective**	Treatment experienced Switched from: -Not mentioned	25 pts with M184V detected at baseline on NRTI-only background regimens: -DTG: n=13/32 (41%) -RAL: n=12/32 (38%)	DTG + FTC/3TC + (ABC 15%, TFV 62%, AZT 23%) Or, RAL + FTC/3TC + (ABC 50%, TFV 33%, AZT 17%)	Not mentioned for subgroup From parent study (SAILING): VL <50,000 c/mL: -n=503/715 (70%)	Percentage of population with protocol-defined VF (defined as VL decrease by <1 log10 c/mL unless <400 c/mL by wk 16 or VL ≥400 c/mL on or after wk 24)	Proportion of pts with protocol-defined VF: -DTG n=0/13 (0%) vs. RAL n=4/12 (33%) (p=0.026) 48 wks (end of trial)
Acosta (2019)[14] **n=565** **M184V: n=81** **Prospective**	Treatment experienced Switched from: -DTG + TFV/FTC: 100%	81 pts with M184V/I: -184V alone: n=71 -184I alone: n=6 -184V/I: n=4 -BIC: n=47/284 -DTG: n=34/281 Excluded pts with documented resistance or VF to INSTI	DTG + TAF/FTC (n=281) Or, BIC/TAF/FTC (n=284)	VL <50 c/mL: 100% -For ≥3months (if no NRTI resistance) -For ≥6months (if known or suspected NRTI resistance)	Proportion of participants with VF (defined as VL ≥50 c/mL on two consecutive visits with VL ≥200 c/mL at confirmation visit)	Proportion of pts with VL <50 c/mL): -DTG: 91% -BIC: 93% -M184V/I: 100% 48 wks (end of trial)

DISCUSSION

- Studies showed similar rates of viral suppression/virologic failure:
  - In pts with M184V vs. pts without M184V[6,7]
  - With regimens containing <3 fully active drugs vs. ≥3 fully active drugs[4]
- Outcomes and treatment comparisons between studies were highly variable
- 5/11 studies used proviral DNA testing to detect M184V[6,8,9,11,14]
  - Lack of clarity regarding clinical application of proviral testing due to limited use in practice[15]
  - Mutations found in deep sequencing may not be picked up in standard GART testing

LIMITATIONS

- Majority of studies retrospective
- Studies had small sample sizes
- Patients were on different background therapy
- Limited duration of follow-up
- Confounders include: duration of ART, coexisting mutations, methods of mutation detection

CONCLUSIONS

- There is preliminary evidence to support the use of 3-drug regimens containing 3TC/FTC + 1 active NRTI + bPI or medium-high barrier to resistance INSTI (DTG, BIC, EVG) in treatment-experienced PLWH who have the M184V mutation
- Caution is warranted with this approach
- Use of a high-barrier INSTI or bPI-based regimen can be considered as a switch option in virologically suppressed patients along with close monitoring for adherence and virologic failure

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