Poster 2510

Systematic Literature Review of Multiclass Resistance in Heavily Treatment-Experienced Persons With HIV

Josephine Mauskopf,[1] Maria Fernandez,[1] Jade Ghosn,[2,3] Paul E. Sax,[4] Julie Priest,[5] Cindy Garris,[5] Andrew Clark[5]

[1]RTI Health Solutions, Research Triangle Park, NC, USA; [2]Assistance Publique – Hôpitaux de Paris, Service des Maladies Infectieuses et Tropicales, Groupe Hospitalier Paris Nord Val de Seine, site Bichat-Claude Bernard, Paris, France; [3]Université Paris Diderot, INSERM UMR 1137 IAME, PRES Sorbonne Paris Cité, Paris, France; [4]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [5]ViiV Healthcare, Research Triangle Park, NC, USA

Julie Priest
Research Triangle Park, NC USA
Julie.L.Priest@ViiVHealthcare.com

Introduction

- Treatment of human immunodeficiency virus (HIV) infection requires use of two or three antiretroviral (ARV) drugs from multiple classes to fully suppress virus replication and prevent the development of drug resistance, due to HIV's high mutation rate.[1,2]
- The approval of integrase strand transfer inhibitors (INSTIs) in 2007–2008 in the USA and EU provided a new treatment option to achieve virus suppression (VS) in individuals with three-class resistance to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs).[3,4]
- However, even with the introduction of INSTI-based regimens, the achievement of full VS is rarely possible in heavily treatment-experienced (HTE) individuals who have multiclass resistance, tolerability issues, and/or contraindications.[2]
- This systematic literature review (SLR) estimates the change in prevalence of multiclass resistance since the introduction of INSTI-based regimens.

Methods

Data source and search strategy

- A SLR using PubMed, Embase, and the Cochrane Library of English language articles published since January 2008 was conducted on May 3, 2018 and updated on February 8, 2019.
- Bibliographies of existing SLRs, websites of European and International organizations reporting data on HIV and acquired immune deficiency syndrome (AIDS), and conference abstracts from 2016 through 2019 were also searched to identify studies.

Eligibility criteria and study selection

- Eligible studies included:
  - Reports on people with HIV infection who were HTE and infected perinatally or as adults.
  - Reports on people who were three-class (or greater) experienced, including the NRTI, NNRTI, PI, and INSTI classes; C-C chemokine receptor type 5 antagonists; and fusion inhibitors.
  - Reports on multiclass (three-class or greater) resistance using any type of resistance definition (e.g., resistance to one drug or resistance to all drugs in class; different algorithms for determining resistance) and resistance tests.
  - Study origin from Western Europe, Australia, Canada, or the USA.
  - Not a comment, letter, editorial, case report, or clinical trial article.
- All studies not meeting these criteria or which included small studies were excluded.
- Eligibility was assessed by two of the authors independently, discrepancies were reconciled by a third author.

Data collection

- The information on study design; populations; definition of resistance, genotypic or phenotypic resistance testing; resistance algorithms; risk factors for multiclass resistance; and prevalence rates of multiclass resistance were extracted.
- Data were independently checked for accuracy by two reviewers.

Risk of bias

- The risk of bias in individual studies was assessed by using the quality assessment checklist for prevalence studies recommended by Hoy et al. (2012).[5]
- Quality assessments were carried out by one reviewer and quality checked by a second reviewer.

Results

Included studies

- A total of 441 unique articles were identified, 343 were excluded during level 1 screening and 61 were excluded during level 2 full-text review (**Figure 1**).
- In total, 34 articles (USA: 11; Canada: 3; Australia: 1; Western Europe: 19) met the inclusion criteria.
- Three studies met the inclusion criteria but were not included in the extraction analysis; two evaluated tropic virus but did not provide data on multiclass resistance and one was an abstract, which did not provide enough detail for inclusion.

Prevalence of three-class resistance to NRTIs+NNRTIs+PIs

- Based on five studies (USA and Canada), there was a modest decrease in the prevalence of resistance to NRTIs+NNRTIs+PIs, the lowest prevalence of resistance ranging from 8.3% in 2009 to 6.7% in 2014 (**Figure 2**).
- In those studies in Figure 3 in Western Europe that presented results for more than one year, a decrease in three-class resistance was recently shown.
- The single study from Australia demonstrated a reduction in resistance, from 16.4% in 2004 to 1.2% in 2013.
- Reasons identified for a decrease in resistance included the availability of new ARV agents, improved ARV therapy (ART) sequencing strategies and earlier use of genotype testing.

Prevalence of four-class resistance to NRTIs+NNRTIs+PIs+INSTIs

- Based on seven studies (USA: 6; France: 1), the prevalence of four-class resistance (including INSTIs) with virologic failure since 2009 is approximately 2%, with lower rates reported in more recent years (**Figure 4**).

Figure 1. PRISMA Diagram

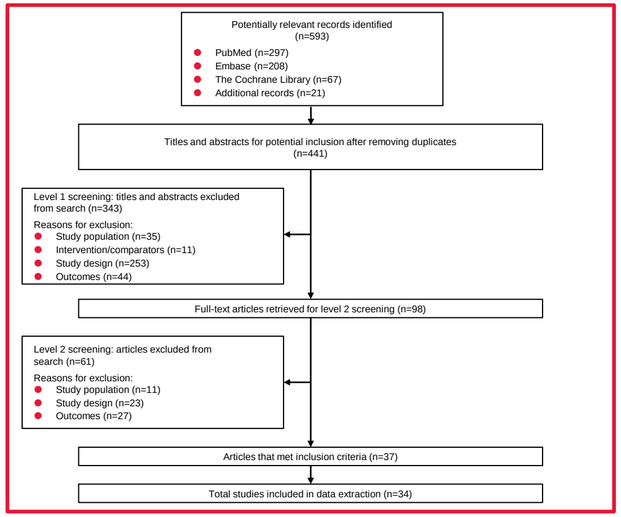
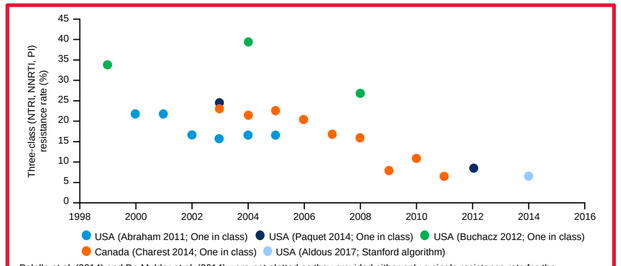


Figure 2. Resistance Rates to Three-Classes (NRTIs+NNRTIs+PIs) in the USA and Canada



Palella et al. (2014) and De Mulder et al. (2014) were not plotted as they provided either only a single resistance rate for the 1999 to 2008 period or corresponded to a resistance rate for a small study of children (n=37), respectively.

Figure 3. Resistance Rates to Three-Classes (NRTIs+NNRTIs+PIs) in Western Europe

Study	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Resistance[d]
France (Assoumou 2017)														0.9					0.8	All in class
Portugal (Vercauteren 2013)						6.9		6.0		3.7		1.6		0.6						≤1 active drug
Sweden (Bontell 2013)		0.26	0.47	0.33	0.7	1.47	1.05	0.8	0.76	0.61	0.4	0.19	0.17	0.09	0.12	0.06				All in class
EU (7 countries; De Luca 2013)		0.0								3.0[a]										All in class
EU (7 countries; De Luca 2013)	2.1 (last genotype); 3.2 (cumulative genotype)																			All in class
EU (7 countries; De Luca 2013)	16.3																			One in class
EU (7 countries; Prosperi 2011)	17.1																			One in class
EU, Israel, Argentina (Cozzi-Lepri 2008)	12 (only major PI mutations); 21 (major and minor[e] mutations)																			One in class
Germany (Schmidt 2014)	15.6																			NR (IAS list)
Italy (Di Giambenedetto 2008)	22																			One in class
Italy (Bracciale 2009)	22																			One in class
Italy (Di Giambenedetto 2009)	16										27									One in class
Italy (Di Giambenedetto 2011)												21		14						One in class
Spain (De Mulder 2012)[b]														21						NR
Spain (Rojas 2015)[b]	24.4																			One in class
Spain and UK (Garcia 2011)	26.9 (last genotype); 46.3 (cumulative genotype)																			NR (Stanford)
Switzerland (Von Wyl 2009)	5.4																			One in class
Switzerland (Scherrer 2016)				9																One in class
UK (Jones 2008)[c]	6.6 (major and minor[e] mutations)																			One in class
UK/Ireland (Foster 2009)[b]	16																			One in class

[a]Value using last genotype (4.5% using cumulative genotype); [b]pediatric patients; [c]included ART-naïve patients; [d]all in class refers to resistance to all members of the therapeutic class whereas one in class refers to resistance to at least one drug per therapeutic class [e]includes minor PI mutations. IAS, International AIDS Society; NR, not reported.

Figure 4. Resistance Rates to Four-Classes (NRTI+PI+NNRTI+INSTI)

Study	2009	2010	2011	2012	2013	2014	2015	2016	Resistance
France (Assoumou 2017)						0.3			All in class (major INSTI mutations)
USA (Hurt 2014)	2.3								Major INSTI resistance mutations
USA (Aldous 2017)						0.4			Stanford algorithm (cumulative genotype)[a]
USA (Menza 2017)	0.3								Major INSTI resistance mutations
USA (Brown 2017)						1			Major INSTI resistance mutations[b]
USA (Davy 2017)							1		One in class (major mutations)[c]
USA (Wang 2016)	1.6								Stanford (1 major mutation/class)

[a]The 2014 Stanford HIV database genotypic resistance interpretation algorithm (including intermediate and high-level resistance mutations) was used to estimate the prevalence of resistance; [b]no mutations were observed in patients treated with dolutegravir; [c]resistance to three or more classes.

Conclusions

- This study demonstrated that the prevalence of multiclass resistance has decreased over the past decade, with three-class resistance declining and four-class resistance a rarity (≤2%).
- These results are consistent with previous SLRs in Quebec, Canada, and the USA of three-class resistance to NRTI, NNRTI, and PI, which noted a decline in resistance since 2001 and 2003, respectively, largely associated with the introduction of new ART regimens.[6,7]
- The results of this SLR should be considered in the context of the limitations of the studies identified, including heterogeneity in viral load resistance testing, use of ARV drugs prior to testing, methods for estimating resistance, and the definition of multiclass drug resistance.
- Although prevalence of multiclass resistance is low in the modern treatment era, there remains a population of heavily treatment-experienced patients with multiple drug resistance who have no viable options.

Disclosures

JM and MF are employees of RTI-Health Solutions, an organization funded by ViiV Healthcare to conduct this research work. JP, CG, and AC are employees of ViiV Healthcare and own stock in GlaxoSmithKline as part of their employment. JG has nothing to disclose. PES is a Scientific Advisory Board member/Consultant for Gilead, GSK/ViiV, Merck, Janssen, receives research support from GSK/ViiV, Gilead, Merck, and holds editorial positions with UpToDate, Medscape, NEJM Journal Watch, Open Forum Infectious Diseases

Acknowledgments

This study (ID: 0305013) was funded by ViiV Healthcare.
Editorial support was provided by Liz Morgan, PhD, at Fishawack Indicia Ltd, UK, and was funded by ViiV Healthcare.

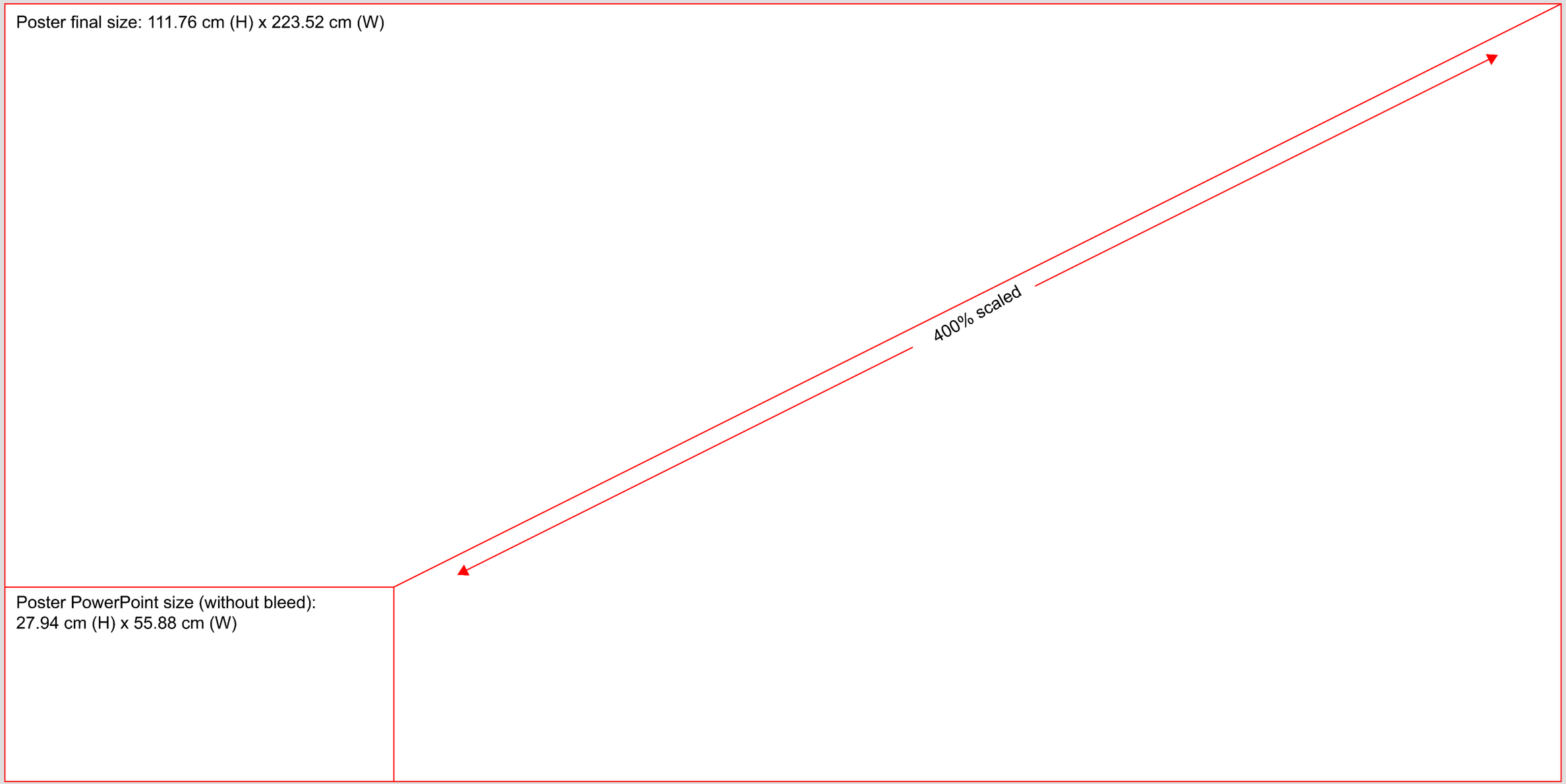
References

1. Tang MW, Shafer RW. *Drugs* 2012;72(9):e1–25; **2.** National Institute for Health. 2019. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV; **3.** Merck & Co., Inc. 2019 Raltegravir Highlights of Prescribing Information; **4.** Merck & Co., Inc. 2019 Raltegravir Summary of Product Characteristics; **5.** Hoy D, et al. *J Clin Epidemiol* 2012;65(9):934–9; **6.** Charest H, et al. *PLoS One* 2014;9(10):e109420; **7.** Paquet AC, et al. *Antivir Ther* 2014;19(4):435–41.

Poster presented at IDWeek 2019, October 2–6, Washington, DC, USA

Poster wall: 121.92 cm (H) x 243.84 cm (W)

Poster final size: 111.76 cm (H) x 223.52 cm (W)



Poster PowerPoint size (without bleed):
27.94 cm (H) x 55.88 cm (W)