Published in final edited form as:

AIDS. 2020 November 01; 34(13): 1975–1977. doi:10.1097/QAD.0000000000002665.

Efficacy and Safety of Two-drug Regimens for Treatment of HIV in the Central Nervous System

Dana Gabuzda^a, Justin C. McArthur^b, Scott L. Letendre^c

^aDana-Farber Cancer Institute, Boston, Massachusetts, USA;

^bJohns Hopkins University School of Medicine, Baltimore, MD, USA;

^cUniversity of California, San Diego, San Diego, CA, USA

Keywords

HIV; cerebrospinal fluid; antiretroviral therapy; dual therapy; treatment simplification

HIV can infect the central nervous system (CNS) soon after transmission, and early initiation of antiretroviral therapy (ART) reduces the establishment or persistence of viral reservoirs in the CNS compartment as well as HIV-associated CNS injury [1, 2]. Successful treatment and virus eradication will require approaches that are effective, safe, and durable in the CNS [3, 4]. Despite current ART regimens that suppress HIV RNA in blood to undetectable levels, people with HIV (PWH) differ substantially in HIV RNA concentrations in cerebrospinal fluid (CSF) [5–8]. In most PWH, HIV RNA concentrations in CSF are more than 1 log₁₀ copies/mL lower in CSF than in blood. After initiation of ART, viral suppression in blood is the primary determinant of viral suppression in CSF [5, 7]. During therapy, a minority of PWH have detectable HIV RNA in CSF when HIV RNA in blood is undetectable, a condition termed CSF viral escape that can occur with or without symptoms [6, 9–12]. CSF viral escape is associated with ART drugs that do not achieve therapeutic concentrations in the CNS and/or have reduced efficacy as a consequence of drug resistance mutations, among other factors such as worse immune status [6, 8, 13–15]. Newer ART drugs with higher potency, high genetic barrier to resistance, and longer half-life, such as second-generation integrase strand transfer inhibitors (INSTIs), are more effective at suppressing HIV systemically and typically also do so in the CNS. These attributes have led to efforts to simplify ART regimens to reduce cost, improve medication adherence, and limit toxicities. However, concerns exist that simplification approaches could lead to HIV escape in the CNS or other tissues where drug distribution and efficacy may be suboptimal [3]. Moreover, if simplified regimens have suboptimal efficacy in the CNS, resurgent HIV replication and resulting immune responses could lead to greater risk for CNS complications of HIV disease, particularly cognitive and mood disorders [1, 10, 16, 17].

Correspondence to: Dana Gabuzda, MD, Department of Cancer Immunology and Virology, Dana-Farber Cancer Institute, Center for Life Science 1010, 450 Brookline Avenue, Boston, MA 02215, USA. dana_gabuzda@dfci.harvard.edu.

Conflicts of interest

The authors declare that they have no competing interests

The study by Trunfio *et al.* [18] addresses these concerns by evaluating the efficacy of two-drug ART regimens in the CNS. Trunfio and colleagues analyzed data from a retrospective, cross-sectional study that compared effects of two-drug (n=19) and three-drug (n=78) ART regimens on CSF viral suppression, biomarkers of inflammation and neuronal injury, and neurocognitive performance in adults who had lumbar punctures performed between 2010–2019 [18]. All participants were on the same ART regimen for at least 30 months prior to lumbar puncture and were virally suppressed with plasma HIV RNA below 200 copies/ml for at least 6 months. Two-drug regimens were heterogeneous and included INSTI + protease inhibitor (PI), INSTI+NNRTI, PI+NNRTI, and PI+NRTI regimens. The authors found no statistically significant differences between the two-drug and three-drug regimens with respect to cognitive performance, CSF viral suppression, or biomarkers. These results are consistent with prior work indicating that ART regimens that suppress HIV in blood usually suppress HIV in CSF as well.

While valuable, these findings should be interpreted in the context of their limitations, including the retrospective cross-sectional design and small cohort with only 19 participants on two-drug regimens, some of which are not routinely used in the clinic. Generalizability of findings to the clinic population may be reduced, since lumbar punctures were performed for clinical indications (e.g., possible neurosyphilis). As such, participants may be more likely than the clinic population to have CNS inflammation and CSF viral escape. CSF viral escape was noted in about a fifth of participants irrespective of regimen type. This non-conservative bias may mean that two-drug regimens are even safer in PWH who do not have clinical indications for lumbar puncture. Other limitations include lack of drug resistance genotypes and measurement of HIV RNA only in cell-free CSF. Cell-associated HIV DNA and HIV RNA have been detected with higher prevalence than CSF cell-free HIV RNA among treated patients and the former has been associated with worse neurocognitive outcomes [16]. While Trunfio *et al.* found no difference in biomarkers of CNS injury and neuroinflammation, prospective studies of larger cohorts and long-term follow-up are needed to validate the findings and identify dual regimens with durable safety and efficacy in the CNS. Future studies should also include vertically-infected PWH, since neurocognitive outcomes are worse in those infected as adults.

Although earlier studies suggested that PWH receiving some older two-drug regimens were more likely to have detectable HIV RNA in CSF [3, 19], particularly those including a PI that can have sub-therapeutic concentrations in CSF (e.g. atazanavir) [8, 15, 20], existing trials support non-inferiority of two-drug regimens compared to three-drug regimens up to 48 or 96 weeks in treatment-experienced patients [21–25]. Dual regimens based on contemporary drugs consist of an INSTI (e.g., dolutegravir) and/or boosted PI (e.g., darunavir) with a reverse transcriptase inhibitor such as lamivudine or rilpivirine. While two studies comparing dual to three-drug regimens found no difference in neurocognitive effects [22, 26], there are few data on efficacy and safety of modern dual regimens in the CNS. Concentrations of most ART drugs are significantly lower in CSF than in blood, although drug concentrations in CSF may not accurately reflect those in brain [27]. Concerns about sub-therapeutic drug concentrations in the CNS are mitigated by the knowledge that regimens that suppress HIV RNA in blood typically suppress HIV RNA in CSF, and that reducing ART drug exposure could reduce the risk of neurotoxicity [3, 28]. Moving forward,

identifying dual regimens with optimal efficacy and safety in different clinical settings will be important, particularly for PWH who struggle with medication adherence – those with psychiatric disease, substance abuse, or living with homelessness. Ongoing development and deployment of new longer-acting ART drugs [29], including long-acting oral drugs [30] and monthly injectables, may be useful in these populations. One study with informative results is the LATITUDE trial ([NCT03635788](#)), which compares long-acting injections of rilpivirine and cabotegravir vs. standard oral regimens in PWH with history of suboptimal adherence.

Overall, these reassuring findings reinforce the importance of future studies to evaluate the comparative efficacy and safety of simplified regimens, particularly long-acting injectables, for controlling HIV in the CNS and reducing the risk of ART neurotoxicity. Randomized controlled clinical trials to study simplified regimens for long-term safety and efficacy in the CNS and other compartments in naïve and experienced patients are awaited.

Acknowledgments

D.G., J.C.M., and S.L.L. wrote and edited the manuscript.

Funding: Supported by NIH grants to D.G. (R56 MH115853), J.M. (P30 MH075673, R25 MH080661, PO1 MH105280, and P30 AI094189 (PI R. Chaisson)), and S. L. (K24 MH097673, R01 MH107345, U24 MH83506, P30 MH62512, P50 DA26306, UM1 AI068636, R01 AG063659).

References

1. Brew BJ, Barnes SL. The impact of HIV central nervous system persistence on pathogenesis. *AIDS* 2019; 33 Suppl 2:S113–S121. [PubMed: 31790377]
2. Spudich S, Peterson J, Fuchs D, Price RW, Gisslen M. Potential for early antiretroviral therapy to reduce central nervous system HIV-1 persistence. *AIDS* 2019; 33 Suppl 2:S135–S144. [PubMed: 31789814]
3. Handoko R, Spudich S. Treatment of Central Nervous System Manifestations of HIV in the Current Era. *Semin Neurol* 2019; 39(3):391–398. [PubMed: 31378874]
4. Lewin SR, Mellors JW. HIV persistence in the CNS: the final frontier for a cure? *J Virus Erad* 2016; 2(4):242. [PubMed: 27781108]
5. Anderson AM, Munoz-Moreno JA, McClernon DR, Ellis RJ, Cookson D, Clifford DB, et al. Prevalence and Correlates of Persistent HIV-1 RNA in Cerebrospinal Fluid During Antiretroviral Therapy. *J Infect Dis* 2017; 215(1):105–113. [PubMed: 27789723]
6. Joseph J, Cinque P, Colosi D, Dravid A, Ene L, Fox H, et al. Highlights of the Global HIV-1 CSF Escape Consortium Meeting, 9 June 2016, Bethesda, MD, USA. *J Virus Erad* 2016; 2(4):243–250. [PubMed: 27781109]
7. Livelli A, Vaida F, Ellis RJ, Ma Q, Ferrara M, Clifford DB, et al. Correlates of HIV RNA concentrations in cerebrospinal fluid during antiretroviral therapy: a longitudinal cohort study. *Lancet HIV* 2019; 6(7):e456–e462. [PubMed: 31208949]
8. Mukerji SS, Misra V, Lorenz DR, Uno H, Morgello S, Franklin D, et al. Impact of Antiretroviral Regimens on Cerebrospinal Fluid Viral Escape in a Prospective Multicohort Study of Antiretroviral Therapy-Experienced Human Immunodeficiency Virus-1-Infected Adults in the United States. *Clin Infect Dis* 2018; 67(8):1182–1190. [PubMed: 29617912]
9. Eden A, Nilsson S, Hagberg L, Fuchs D, Zetterberg H, Svennerholm B, et al. Asymptomatic Cerebrospinal Fluid HIV-1 Viral Blips and Viral Escape During Antiretroviral Therapy: A Longitudinal Study. *J Infect Dis* 2016; 214(12):1822–1825. [PubMed: 27683820]
10. Mastrangelo A, Turrini F, de Zan V, Caccia R, Gerevini S, Cinque P. Symptomatic cerebrospinal fluid escape. *AIDS* 2019; 33 Suppl 2:S159–S169. [PubMed: 31789816]

11. Trunfio M, Pinnetti C, Foca E, Bai F, Maffongelli G, Celani L, et al. Cerebrospinal fluid HIV-1 escape according to different thresholds and underlying comorbidities: is it time to assess the definitions? *AIDS* 2019; 33(4):759–762. [PubMed: 30531317]
12. Winston A, Antinori A, Cinque P, Fox HS, Gisslen M, Henrich TJ, et al. Defining cerebrospinal fluid HIV RNA escape: editorial review *AIDS*. *AIDS* 2019; 33 Suppl 2:S107–S111. [PubMed: 31790376]
13. Mukerji SS, Misra V, Lorenz D, Cervantes-Arslanian AM, Lyons J, Chalkias S, et al. Temporal Patterns and Drug Resistance in CSF Viral Escape Among ART-Experienced HIV-1 Infected Adults. *J Acquir Immune Defic Syndr* 2017; 75(2):246–255. [PubMed: 28328546]
14. Nightingale S, Michael BD, Fisher M, Winston A, Nelson M, Taylor S, et al. CSF/plasma HIV-1 RNA discordance even at low levels is associated with up-regulation of host inflammatory mediators in CSF. *Cytokine* 2016; 83:139–146. [PubMed: 27131579]
15. Perez-Valero I, Ellis R, Heaton R, Deutsch R, Franklin D, Clifford DB, et al. Cerebrospinal fluid viral escape in aviremic HIV-infected patients receiving antiretroviral therapy: prevalence, risk factors and neurocognitive effects. *AIDS* 2019; 33(3):475–481. [PubMed: 30702516]
16. Spudich S, Robertson KR, Bosch RJ, Gandhi RT, Cyktor JC, Mar H, et al. Persistent HIV-infected cells in cerebrospinal fluid are associated with poorer neurocognitive performance. *J Clin Invest* 2019; 129(8):3339–3346. [PubMed: 31305262]
17. Joseph SB, Kincer LP, Bowman NM, Evans C, Vinikoor MJ, Lippincott CK, et al. Human Immunodeficiency Virus Type 1 RNA Detected in the Central Nervous System (CNS) After Years of Suppressive Antiretroviral Therapy Can Originate from a Replicating CNS Reservoir or Clonally Expanded Cells. *Clin Infect Dis* 2019; 69(8):1345–1352. [PubMed: 30561541]
18. Trunfio M, Rugge W, Mighetto L, Vai D, Atzori C, Nigra M, et al. Dual Antiretroviral Therapies are Effective and Safe Regimens in the Central Nervous System of Neurologically Symptomatic People Living with HIV. *AIDS* 2020; in press.
19. Mangioni D, Muscatello A, Sabbatini F, Soria A, Rossi M, Bisi L, et al. A case of cerebrospinal fluid viral escape on a dual antiretroviral regimen: worth the risk? *Clin Infect Dis* 2014; 59(11):1655–1656. [PubMed: 25156113]
20. Best BM, Letendre SL, Brigid E, Clifford DB, Collier AC, Gelman BB, et al. Low atazanavir concentrations in cerebrospinal fluid. *AIDS* 2009; 23(1):83–87. [PubMed: 19050389]
21. Cento V, Perno CF. Two-drug regimens with dolutegravir plus rilpivirine or lamivudine in HIV-1 treatment-naïve, virologically-suppressed patients: Latest evidence from the literature on their efficacy and safety. *J Glob Antimicrob Resist* 2020; 20:228–237. [PubMed: 31446092]
22. Mondì A, Fabbiani M, Ciccarelli N, Colafigli M, D'Avino A, Borghetti A, et al. Efficacy and safety of treatment simplification to atazanavir/ritonavir + lamivudine in HIV-infected patients with virological suppression: 144 week follow-up of the AtLaS pilot study. *J Antimicrob Chemother* 2015; 70(6):1843–1849. [PubMed: 25885326]
23. Moreno S, Perno CF, Mallon PW, Behrens G, Corbeau P, Routy JP, et al. Two-drug vs. three-drug combinations for HIV-1: Do we have enough data to make the switch? *HIV Med* 2019; 20 Suppl 4:2–12.
24. Pasquau J, de Jesus SE, Arazo P, Crusells MJ, Rios MJ, Lozano F, et al. Effectiveness and safety of dual therapy with rilpivirine and boosted darunavir in treatment-experienced patients with advanced HIV infection: a preliminary 24 week analysis (RIDAR study). *BMC Infect Dis* 2019; 19(1):207. [PubMed: 30819101]
25. Pierone G, Henegar C, Fusco J, Vannappagari V, Aboud M, Ragone L, et al. Two-drug antiretroviral regimens: an assessment of virologic response and durability among treatment-experienced persons living with HIV in the OPERA((R)) Observational Database. *J Int AIDS Soc* 2019; 22(12):e25418. [PubMed: 31802641]
26. Perez-Valero I, Pasquau J, Rubio R, Rivero A, Santos J, Sanz J, et al. Neurocognitive safety after 96 weeks on dual therapy with atazanavir/ritonavir plus lamivudine: results of the neurocognitive substudy of the SALT randomized clinical trial. *J Antimicrob Chemother* 2018; 73(9):2444–2451. [PubMed: 29897573]

27. Srinivas N, Rosen EP, Gilliland WM Jr., Kovarova M, Remling-Mulder L, De La Cruz G, et al. Antiretroviral concentrations and surrogate measures of efficacy in the brain tissue and CSF of preclinical species. *Xenobiotica* 2019; 49(10):1192–1201. [PubMed: 30346892]
28. Lanman T, Letendre S, Ma Q, Bang A, Ellis R. CNS Neurotoxicity of Antiretrovirals. *J Neuroimmune Pharmacol* 2019.
29. Letendre SL, Mills A, Hagins D, Swindells S, Felizarta F, Devente J, et al. Pharmacokinetics and antiviral activity of cabotegravir and rilpivirine in cerebrospinal fluid following long-acting injectable administration in HIV-infected adults. *J Antimicrob Chemother* 2020; 75(3):648–655. [PubMed: 31873746]
30. Kirtane AR, Abouzid O, Minahan D, Bense T, Hill AL, Selinger C, et al. Development of an oral once-weekly drug delivery system for HIV antiretroviral therapy. *Nat Commun* 2018; 9(1):2. [PubMed: 29317618]