

Better drugs for Lyme disease: focus on the spirochete

Raphael B Stricker¹
Marianne J Middelveen²

¹Union Square Medical Associates, San Francisco, CA, USA; ²Atkins Veterinary Services, Calgary, AB, Canada

→ Video abstract



Point your Smartphone at the code above. If you have a QR code reader the video abstract will appear. Or use: <http://youtu.be/Bjns5Bq-Hj08>

Abstract: Twenty-five years ago, the AIDS epidemic was wreaking havoc around the world. Although “HIV denialists” threatened to undermine research efforts to combat the epidemic, development of targeted antiviral therapy eventually provided effective treatment for the disease. Now the Lyme disease epidemic is wreaking havoc around the world, and “Lyme denialists” are undermining efforts to combat the epidemic. Drawing on our experience with the AIDS epidemic, there is a significant need to develop targeted therapy to control the Lyme disease epidemic.

Keywords: HIV/AIDS, Lyme disease, *Borrelia burgdorferi*, tick-borne disease, designer drugs

It was 1993. The AIDS epidemic was in full swing with nearly 25,000 new cases diagnosed annually in the USA.¹ Repurposed chemotherapy drugs such as zidovudine (AZT) and other nucleoside analogs were failing to control the HIV-induced disease, and in the absence of effective therapy, over 80% of AIDS patients were using alternative and complementary treatments in a desperate attempt to keep their shattered lives going.² Citing flawed concepts of retroviral pathology, a small group of “HIV denialists” was whispering that HIV was not the cause of AIDS and that the medical community should turn away from antiretroviral therapy and look elsewhere for better AIDS treatment.³

Amid this cacophony, the voice of AIDS researcher David Ho helped to refocus the attack against AIDS.⁴ In a memorable quote, Ho stated his case quite simply: “It’s the virus, stupid!” The emphasis on targeting HIV encouraged the pharmaceutical industry to redouble its efforts to develop better antiretroviral therapy. Within 3 years, pharmaceutical giants Roche Holding AG (Basel, Switzerland), Merck & Co. (Kenilworth, NJ, USA) and Abbott Laboratories (Chicago, IL, USA) had produced highly active antiretroviral protease inhibitors, and the reversal of AIDS mortality had begun.¹ The rest is history.

Fast forward 25 years to 2018. The Lyme disease epidemic is in full swing with more than 300,000 new cases diagnosed annually in the USA.⁵ Early-generation antibiotics such as tetracyclines and penicillins are failing to control the tick-borne disease, and in the absence of effective therapy more than two-thirds of Lyme disease patients are using alternative and complementary treatments in a desperate attempt to put their shattered lives back together.⁶ Citing flawed studies of antibiotic therapy, a small group of “Lyme denialists” has proclaimed that *Borrelia burgdorferi*, the spirochetal agent of Lyme disease, is not the cause of persistent symptoms in the growing number of patients suffering from chronic illness.⁷ Confronted with the controversy over chronic Lyme disease, the pharmaceutical industry has turned its back on suffering patients

Correspondence: Raphael B Stricker
Union Square Medical Associates, 450
Sutter Street, Suite 1504,
San Francisco, CA 94108, USA
Tel +1 415 399 1035
Email rstricker@usmamed.com



and their doctors who are trying to fight the disease. In the absence of more effective therapy, health care organizations and insurers have become complacent about inadequate treatment for Lyme disease.^{6,8}

Amid this medical disaster, two recent reports should help to refocus the attack against the Lyme spirochete. The report by Cabello et al⁹ highlights the ability of *Borrelia* “sleeper cells” to survive for extended periods in both the tick vector and vertebrate host using a “stringent response” that has been described in other bacterial infections.¹⁰ The stringent response in *Borrelia* is mediated by an “alarmone”, (p)ppGpp, that is postulated to be the master regulator of this function in the Lyme spirochete, and the complex metabolic and morphologic changes involved in the *Borrelia* stringent response allow the spirochete to cope with otherwise lethal nutritional deprivation, antimicrobial therapy, and host immunological defenses.⁹ The detailed adaptive functions described by Cabello et al help to explain tolerance to antibiotics in *Borrelia* “persister cells” studied in vitro by other researchers,^{11,12} and recognition of “sleeper cells” supports the likelihood of persistent *Borrelia* infection in patients who suffer from chronic Lyme disease symptoms despite conventional antibiotic therapy.¹³

The second report by Middelveen et al¹⁴ demonstrates that Lyme disease patients are infected with viable *Borrelia* spirochetes that can be cultured from various body fluids, even if the patients are taking conventional antibiotic therapy. To address skepticism from “Lyme denialists,”¹⁵ *Borrelia* cultures were tested in a blinded manner in laboratories located in Canada, Australia, and the USA using different molecular techniques, and the results were validated in a completely independent laboratory.¹⁴ The study confirms and extends similar reports of viable *Borrelia* spirochetes in treated nonhuman primates¹⁶ and in Lyme disease patients with persistent symptoms from Europe^{17,18} and the USA,^{19–21} and the results emphasize the ability of *Borrelia* spirochetes to evade antibiotic therapy under clinical conditions.^{14,22} The finding of live *Borrelia* spirochetes in semen and vaginal secretions is particularly disturbing because it suggests that Lyme disease could be sexually transmitted in a manner similar to syphilis, chlamydia, HIV, Ebola, and Zika virus.^{23–27}

What does this mean? It is time for the pharmaceutical industry to train its sights on *Borrelia burgdorferi* in the same way that it has attacked HIV and hepatitis C virus (HCV). Because a safe and effective Lyme disease vaccine is presently out of reach for technical reasons,^{28,29} we need targeted designer drugs to treat the Lyme spirochete, and we can use the HIV and HCV models to develop these drugs.⁸ Designer drugs would avoid the overuse of 60-year-old antibiotics that

are marginally effective to begin with, and targeted therapy would provide more rational treatment for the tick-borne disease. Development of designer drugs for *Borrelia* would also open the door for research into more effective treatment for tick-borne bacterial, protozoal, and viral coinfections.^{30–32} Furthermore, if *Borrelia* is proven to be sexually transmitted, targeted drug therapy would theoretically be more effective in preventing the spread of the spirochete, given the success with preexposure and postexposure prophylaxis for HIV disease.^{33,34}

To paraphrase David Ho, “It’s the spirochete, stupid!” We must find better ways to kill the Lyme spirochete with targeted designer drugs.

Disclosure

The authors report no conflicts of interest in this work.

References

- Osmond DH. Epidemiology of HIV/AIDS in the United States. HIV InSite Knowledge Base Chapter; 2003. Available from: <http://hivinsite.ucsf.edu/InSite?page=kb-01-03#S1.4X>. Accessed August 26, 2018.
- Brauchli P, Reuteler I, Bürki B, Saller R. Use of complimentary medical therapies in HIV/AIDS in Switzerland. *Schweiz Med Wochenschr*. 1996;126(30):1297–1305.
- Duesberg PH. AIDS epidemiology: inconsistencies with human immunodeficiency virus and with infectious disease. *Proc Natl Acad Sci U S A*. 1991;88(4):1575–1579.
- Cohen J. AIDS research. Keystone’s blunt message: ‘it’s the virus, stupid’. *Science*. 1993;260(5106):292–293.
- Stone BL, Tourand Y, Brissette CA. Brave new worlds: the expanding universe of Lyme disease. *Vector Borne Zoonotic Dis*. 2017;17(9):619–629.
- Johnson L, Wilcox S, Mankoff J, Stricker RB. Severity of chronic Lyme disease compared to other chronic conditions: a quality of life survey. *PeerJ*. 2014;2:e322.
- Delong AK, Blossom B, Maloney EL, Phillips SE. Antibiotic retreatment of Lyme disease in patients with persistent symptoms: a biostatistical review of randomized, placebo-controlled, clinical trials. *Contemp Clin Trials*. 2012;33(6):1132–1142.
- Stricker RB, Johnson L. Lyme disease: the promise of Big Data, companion diagnostics and precision medicine. *Infect Drug Resist*. 2016;9:215–219.
- Cabello FC, Godfrey HP, Bugrysheva JV, Newman SA. Sleeper cells: the stringent response and persistence in the *Borrelia burgdorferi* enzootic cycle. *Environ Microbiol*. 2017;19(10):3846–3862.
- Godfrey HP, Bugrysheva JV, Cabello FC. The role of the stringent response in the pathogenesis of bacterial infections. *Trends Microbiol*. 2002;10(8):349–351.
- Feng J, Shi W, Zhang S, Zhang Y. Persister mechanisms in *Borrelia burgdorferi*: implications for improved intervention. *Emerg Microbes Infect*. 2015;4(8):e51.
- Sharma B, Brown AV, Matluck NE, Hu LT, Lewis K. *Borrelia burgdorferi*, the causative agent of Lyme disease, forms drug-tolerant persister cells. *Antimicrob Agents Chemother*. 2015;59(8):4616–4624.
- Stricker RB, Johnson L. Persistent infection in chronic Lyme disease: does form matter? *Res J Infect Dis*. 2013;1:2.
- Middelveen MJ, Sapi E, Burke J, et al. Persistent *Borrelia* infection in patients with ongoing symptoms of Lyme disease. *Healthcare*. 2018;6(2):33.
- Wormser GP, Shapiro ED, Strle F. Studies that report unexpected positive blood cultures for Lyme *Borrelia* - are they valid? *Diagn Microbiol Infect Dis*. 2017;89(3):178–181.

16. Embers ME, Hasenkampf NR, Jacobs MB, et al. Variable manifestations, diverse seroreactivity and post-treatment persistence in non-human primates exposed to *Borrelia burgdorferi* by tick feeding. *PLoS One*. 2017;12(12):e0189071.
17. Maraspin V, Ogrinc K, Ružič-Sabljic E, Lotrič-Furlan S, Strle F. Isolation of *Borrelia burgdorferi* sensu lato from blood of adult patients with borreliac lymphocytoma, Lyme neuroborreliosis, Lyme arthritis and acrodermatitis chronica atrophicans. *Infection*. 2011;39(1):35–40.
18. Lenormand C, Jaulhac B, Debarbieux S, et al. Expanding the clinicopathological spectrum of late cutaneous Lyme borreliosis (acrodermatitis chronica atrophicans [ACA]): A prospective study of 20 culture- and/or polymerase chain reaction (PCR)-documented cases. *J Am Acad Dermatol*. 2016;74(4):685–692.
19. Rudenko N, Golovchenko M, Vancova M, Clark K, Grubhoffer L, Oliver JH. Isolation of live *Borrelia burgdorferi* sensu lato spirochaetes from patients with undefined disorders and symptoms not typical for Lyme borreliosis. *Clin Microbiol Infect*. 2016;22(3):267.e9–267.e15.
20. Clark KL, Leydet B, Hartman S. Lyme borreliosis in human patients in Florida and Georgia, USA. *Int J Med Sci*. 2013;10(7):915–931.
21. Sapi E, Pabbati N, Datar A, Davies EM, Rattelle A, Kuo BA. Improved culture conditions for the growth and detection of *Borrelia* from human serum. *Int J Med Sci*. 2013;10(4):362–376.
22. Middelveen MJ, Bandoski C, Burke J, et al. Exploring the association between Morgellons disease and Lyme disease: identification of *Borrelia burgdorferi* in Morgellons disease patients. *BMC Dermatol*. 2015;15:1.
23. Stricker RB, Middelveen MJ. Sexual transmission of Lyme disease: challenging the tickborne disease paradigm. *Expert Rev Anti Infect Ther*. 2015;13(11):1303–1306.
24. Radolf JD, Deka RK, Anand A, Šmajš D, Norgard MV, Yang XF. *Treponema pallidum*, the syphilis spirochete: making a living as a stealth pathogen. *Nat Rev Microbiol*. 2016;14(12):744–759.
25. Mestecky J, Moldoveanu Z, Russell MW. Immunologic uniqueness of the genital tract: challenge for vaccine development. *Am J Reprod Immunol*. 2005;53(5):208–214.
26. Fischer WA, Wohl DA. Confronting Ebola as a sexually transmitted infection. *Clin Infect Dis*. 2016;62(10):1272–1276.
27. Moreira J, Peixoto TM, Siqueira AM, Lamas CC. Sexually acquired Zika virus: a systematic review. *Clin Microbiol Infect*. 2017;23(5):296–305.
28. Marks DH. Neurological complications of vaccination with outer surface protein A (OspA). *Int J Risk Saf Med*. 2011;23(2):89–96.
29. Stricker RB, Johnson L. Lyme disease vaccination: safety first. *Lancet Infect Dis*. 2014;14(1):12.
30. Zhang XC, Yang ZN, Lu B, Ma XF, Zhang CX, Xu HJ. The composition and transmission of microbiome in hard tick, *Ixodes persulcatus*, during blood meal. *Ticks Tick Borne Dis*. 2014;5(6):864–870.
31. Tokarz R, Williams SH, Sameroff S, Sanchez Leon M, Jain K, Lipkin WI. Virome analysis of *Amblyomma americanum*, *Dermacentor variabilis*, and *Ixodes scapularis* ticks reveals novel highly divergent vertebrate and invertebrate viruses. *J Virol*. 2014;88(19):11480–11492.
32. Pedroni MJ, Vidadala RS, Choi R, et al. Bumped kinase inhibitor prohibits egression in *Babesia bovis*. *Vet Parasitol*. 2016;215:22–28.
33. Özdener AE, Park TE, Kalabalik J, Gupta R. The future of pre-exposure prophylaxis (PrEP) for human immunodeficiency virus (HIV) infection. *Expert Rev Anti Infect Ther*. 2017;15(5):467–481.
34. Mayer KH, Jones D, Oldenburg C, et al. Optimal HIV postexposure prophylaxis regimen completion with single tablet daily elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine compared with more frequent dosing regimens. *J Acquir Immune Defic Syndr*. 2017;75(5):535–539.

Infection and Drug Resistance

Publish your work in this journal

Infection and Drug Resistance is an international, peer-reviewed open-access journal that focuses on the optimal treatment of infection (bacterial, fungal and viral) and the development and institution of preventive strategies to minimize the development and spread of resistance. The journal is specifically concerned with the epidemiology of antibiotic

resistance and the mechanisms of resistance development and diffusion in both hospitals and the community. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/infection-and-drug-resistance-journal>

Dovepress