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Review

# Tolerance to Trypanosomatids: A Threat, or a Key for Disease Elimination?

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**So far, research on trypanosomatid infections has been driven by 'disease by disease' approaches, leading to different concepts and control strategies. It is, however, increasingly clear that they share common features such as the ability to generate long-lasting asymptomatic infections in their mammalian hosts. Trypanotolerance, long integrated in animal African trypanosomiasis control, historically refers to the ability of cattle breeds to limit *Trypanosoma* infection and pathology, but has only recently been recognized in humans. Whilst trypanotolerance is absent from the vocabulary on leishmaniasis and Chagas disease, asymptomatic infections also occur. We review the concept of trypanotolerance across the trypanosomatids and discuss the importance of asymptomatic carriage in the current context of elimination.**

## What is Trypanotolerance?

African and American trypanosomes, together with *Leishmania* species, belong to the Trypanosomatidae family in the Kinetoplastid order. Most are cyclically transmitted by insect vectors and infect mammals including humans. They induce a large range of clinical symptoms (Figure 1), are widely distributed around the world although active transmission occurs in the poorest countries (Figure 2), and display important biological differences in terms of tissue and cellular localization in their mammalian hosts. African trypanosomes are extracellular parasites found in several body fluids such as the blood, the lymph, or the cerebrospinal fluid. *Leishmania* species are intracellular parasites of the monocyte–macrophage lineage cells and can be found in skin lesions, lymph nodes, spleen, or bone marrow. The situation for *Trypanosoma cruzi* appears more complex with both trypomastigote extracellular forms circulating in the mammal blood and intracellular forms that can invade a variety of cells (including reticuloendothelial and myocardial cells) and organs (skin, muscles, liver, nervous system). Despite these differences, a common feature between these different trypanosomatids is their ability to induce chronic asymptomatic infections. Trypanotolerance, the ability to control the proliferation of parasites and to limit their pathological effects, is widely employed in the context of African animal trypanosomiasis (AAT) [1,2]. However, little attention has been given to the phenomenon for the other trypanosomatids species causing human disease [human African trypanosomiasis (HAT), leishmaniases, and Chagas disease], although subclinical or asymptomatic infections also occur in these diseases.

The mechanisms underlying host control of infections by trypanosomatids are starting to be understood and may provide new therapeutic or prophylactic targets for these neglected

### Trends

Trypanotolerance, which describes the ability of animals to limit the deleterious effects of African trypanosomes, also exists for other diseases caused by parasite species from the *Trypanosomatidae* family: human African trypanosomiasis (sleeping sickness), American trypanosomiasis (Chagas disease), and leishmaniasis.

Asymptomatism (or paucisymptomatism) and chronicity appear more widespread than previously thought and should be taken into account for disease control.

Genetic mechanisms controlling host tolerance to trypanosomatids parasites are progressively understood and reveal some common features highlighted here.

Transversal research approaches on vector-borne diseases due to trypanosomatids should help to propose new tools for their elimination.

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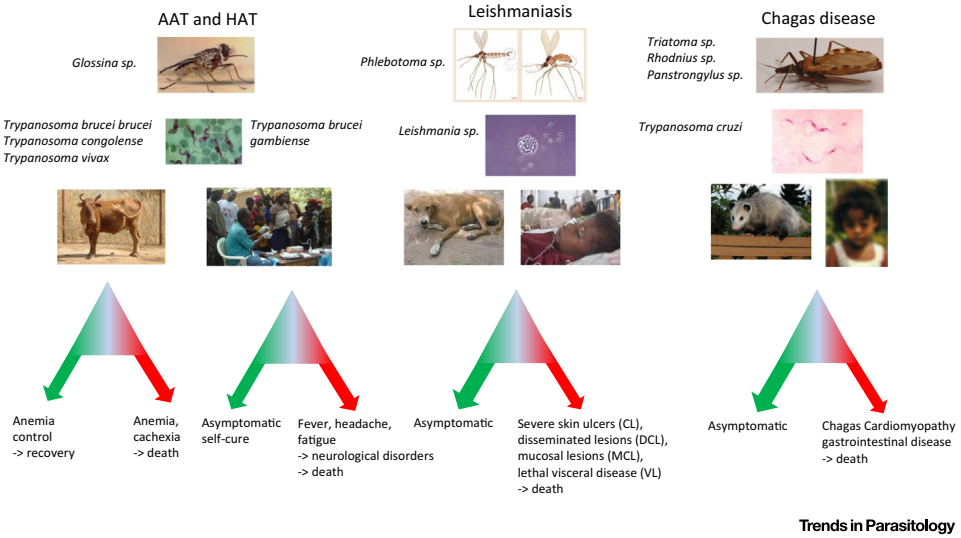


Figure 1. Diseases Due to Trypanosomatids: Vectors, Parasites, and Main Symptoms. For each disease, a picture of the vectors and of the parasite involved is presented, and a gradation of the symptoms that allows the shared features of the outcome of these diseases to be seen. Abbreviations: HAT, human African trypanosomiasis; AAT, animal African trypanosomiasis.

tropical diseases. The existence of asymptomatic carriers may undermine the impact of control programs. This review focuses on the concept of trypanotolerance across the trypanosomatids and discusses the importance of asymptomatic carriage in the context of elimination of these diseases by 2020.

## Trypanotolerance in African Animal Trypanosomiasis

Trypanotolerance in AAT (Box 1) has been recognized for more than one century [3]. Symptoms of AAT in livestock due to *Trypanosoma congolense*, *Trypanosoma vivax*, or *Trypanosoma brucei brucei* (the most widespread pathogenic trypanosomes in Africa) include anemia, fever, whimpering, edemas, progressive emaciation leading to cachexia, and death, if not treated. Trypanotolerance has been observed in West African bovines and was defined as 'the ability of some livestock breeds to survive, reproduce and produce in tsetse-trypanosome infested areas where others cannot, without recourse to use of chemical drug' [1,4]. Hence, trypanotolerance corresponds to the definition of tolerance given in Gibson and Bishop [5] as the ability of an individual host to suffer little or no harm despite infection. Examples of trypanotolerant breeds include the well-known N'Dama, the short-horn taurine Baoulé and Lagune, whereas Zebu breeds and exotic taurine breeds are susceptible [1,6–9]. The trypanotolerant phenotype displays a dichotomy between breeds (tolerant or not tolerant), but also shows variability between individuals within a breed [10].

Trypanotolerant cattle are the only breeds that can be raised in areas with high AAT incidence [1,11]. They are usually crossed by farmers with susceptible zebu to provide cattle with intermediate features regarding trypanotolerance, but also size–weight, milk, and meat production [9,11,12]. This enables them to be raised in AAT areas in combination with integrated control strategies against other pathogens [13]. However, crossings have generally been done without any knowledge on the genes and polymorphisms underlying trypanotolerance, and such knowledge could be used in the future to develop more adapted breeds, to cope both with trypanosomes and a poor production level [14,15].