



Review

Reducing the global burden of HTLV-1 infection: An agenda for research and action



Luc Willems^{a, z, *}, Hideki Hasegawa^{b, z}, Roberto Accolla^c, Charles Bangham^d, Ali Bazarbachi^e, Umberto Bertazzoni^f, Anna Barbara de Freitas Carneiro-Proietti^g, Hua Cheng^h, Luigi Chieco-Bianchiⁱ, Vincenzo Ciminaleⁱ, Jordana Coelho-dos-Reis^j, José Esparza^h, Robert C. Gallo^h, Antoine Gessain^k, Eduardo Gotuzzo^l, William Hall^m, Joseph Harfordⁿ, Olivier Hermine^o, Steven Jacobson^p, Beatrice Macchi^q, Calum Macpherson^r, Renaud Mahieux^s, Masao Matsuoka^t, Edward Murphy^u, Jean-Marie Peloponese^v, Viviana Simon^w, Yutaka Tagaya^h, Graham P. Taylor^d, Toshiki Watanabe^x, Yoshihisa Yamano^y

^a University of Liege, Belgium

^b National Institute of Infectious Diseases, Tokyo, Japan

^c University of Insubria, Varese, Italy

^d Imperial College, London, UK

^e American University of Beirut, Beirut, Lebanon

^f University of Verona, Verona, Italy

^g Fundação Hemominas, Belo Horizonte, Brazil

^h Institute of Human Virology, Baltimore, USA

ⁱ University of Padova, Padova, Italy

^j René Rachou Research Center, FIOCRUZ, Belo Brazil Horizonte, Brazil

^k Institut Pasteur, Paris, France

^l Tropical Medical Institute Alexander von Humboldt, Lima, Peru

^m Centre for Research in Infectious Disease, Dublin, Ireland

ⁿ National Cancer Institute, NIH, Bethesda, USA

^o Hôpital Necker, Paris, France

^p National Institute of Neurological Disorders and Stroke, NIH, Bethesda, USA

^q University of Rome Tor Vergata, Rome, Italy

^r St. George's University, Grenada

^s Ecole Normale Supérieure de Lyon, Lyon, France

^t Kyoto University, Kyoto, Japan

^u University of California, San Francisco, USA

^v University of Montpellier, Montpellier, France

^w Icahn School of Medicine at Mount Sinai, New York, USA

^x University of Tokyo, Tokyo, Japan

^y St. Marianna University School of Medicine, Kanagawa, Japan

^z Chairs of the HTLV Taskforce of the Global Virus Network, USA

ARTICLE INFO

Article history:

Received 21 October 2016

Accepted 29 October 2016

Available online 11 November 2016

Keywords:

HTLV-1

Vaccine

ABSTRACT

Even though an estimated 10–20 million people worldwide are infected with the oncogenic retrovirus, human T-lymphotropic virus type 1 (HTLV-1), its epidemiology is poorly understood, and little effort has been made to reduce its prevalence. In response to this situation, the Global Virus Network launched a taskforce in 2014 to develop new methods of prevention and treatment of HTLV-1 infection and promote basic research. HTLV-1 is the etiological agent of two life-threatening diseases, adult T-cell leukemia and HTLV-associated myelopathy/tropical spastic paraparesis, for which no effective therapy is currently available. Although the modes of transmission of HTLV-1 resemble those of the more familiar HIV-1, routine diagnostic methods are generally unavailable to support the prevention of new infections. In

* Corresponding author. Molecular and Cellular Epigenetics, Interdisciplinary Cluster for Applied Genoproteomics (GIGA) of University of Liège (ULg), B34, 1 Avenue de l'Hôpital, 4000, Sart-Tilman, Liège, Belgium.

E-mail address: luc.willems@ulg.ac.be (L. Willems).

Contents

1. Introduction: the global burden of HTLV-1 infection	42
2. The HTLV taskforce	42
3. Research priorities and open questions	42
3.1. Review the global prevalence of HTLV-1 infection and identify opportunities and means to expand epidemiological studies	42
3.2. Identify biomarkers to predict disease progression	45
3.3. Develop preventive and therapeutic vaccines	45
3.4. Screen for existing and novel drugs to improve therapy	45
3.5. Perform basic research to unravel mechanisms of viral persistence, replication and pathogenesis to open insights into novel treatments	46
4. Conclusion and perspectives	46
Acknowledgements	47
References	47

1. Introduction: the global burden of HTLV-1 infection

It is estimated that at least 20 million people worldwide are infected with the oncogenic retrovirus, human T-cell leukemia virus type 1 (HTLV-1). The area of highest prevalence is southwestern Japan, but infection is also common in sub-Saharan Africa, the Caribbean islands, and some regions of South America, the Middle East and Austro-Melanesia. Similar to the human immunodeficiency virus (HIV)-1, transmission occurs principally from mother to child, between sexual partners, through contaminated blood products and by needle sharing. Infected individuals are at risk of developing a rapidly progressive malignancy, adult T-cell leukemia (ATL), and a debilitating and sometimes fatal neurologic condition, myelopathy/tropical spastic paraparesis (HAM/TSP). In contrast to HIV-1 and beyond screening serology, only limited diagnostic methods are available, generally for research studies, and little effort has been made to identify infected persons and reduce transmission. No vaccines or fully effective therapies are currently available. A closely related virus, HTLV-2, is present in many world areas (e.g. North and South America, South of Europe, Ireland, Vietnam) and its pathogenic potential needs to be further clarified.

In response to this situation, the Global Virus Network launched a taskforce in 2014 to promote basic research, develop new methods of prevention and treatment of HTLV-1 infection and recommend new public health measures. This article presents the consensus views of taskforce members regarding unsolved or controversial issues that hamper further understanding of HTLV-1 and the development of new approaches for diagnosis, prevention and therapy. For additional information on the molecular mechanisms of pathogenesis, immunological aspects, epidemiology and currently available therapies for HTLV-1 infection, readers are referred to a number of excellent review articles (Bangham et al., 2015; Matsuoka and Jeang, 2007; Pique and Jones, 2012; Murphy, 2016; Gessain and Cassar, 2012; Kato and Akashi, 2015).

2. The HTLV taskforce

The mission of the Global Virus Network is to strengthen medical research and the public health response to viral agents of human disease and to prepare for new pandemic threats

(McSweegan et al., 2015). The GVN includes a number of centers of excellence for research in medical virology across the globe. For further information, readers are referred to the GVN website at <http://gvn.org>.

The HTLV taskforce emerged from an initiative of the GVN on June 17, 2014. The members of the HTLV-1 taskforce are located on Fig. 1 and listed in Table 1.

Consultation among taskforce members has led to the following proposed series of actions to be carried out by researchers in GVN centers of excellence and their scientific collaborators:

- review the global prevalence of HTLV-1 infection and identify opportunities and means to expand epidemiological studies;
- identify biomarkers to predict disease progression;
- develop prophylactic and therapeutic vaccines;
- screen for existing and novel drugs to improve therapy;
- perform basic research to unravel mechanisms of viral infectivity, persistence, replication and pathogenesis to open insights into novel treatments;

These proposed actions are discussed in turn in the following sections.

3. Research priorities and open questions

3.1. Review the global prevalence of HTLV-1 infection and identify opportunities and means to expand epidemiological studies

Regions of high prevalence, including Indonesia, Iran, Africa, Japan, the Caribbean, South America (especially Brazil and Peru), Romania and parts of Australo-Melanesia and the Middle-East have been identified worldwide (Gessain and Cassar, 2012). Although HTLV-1 was discovered in 1979, there is no recommendation for systematic screening worldwide. In particular, HTLV-1 prevalence is still poorly understood in several areas of East and North Africa and most parts of Asia, due mainly to a lack of solid data (Murphy, 2016). Furthermore, HTLV-1 and simian T-lymphotropic virus type 1 (STLV-1) can be considered as a single virus infecting and inducing diseases in two different species (Enose-Akahata et al., 2016). Besides HTLV-1, there is evidence for zoonotic transmission of other primate T-lymphotropic viruses (Filippone et al., 2015; Richard

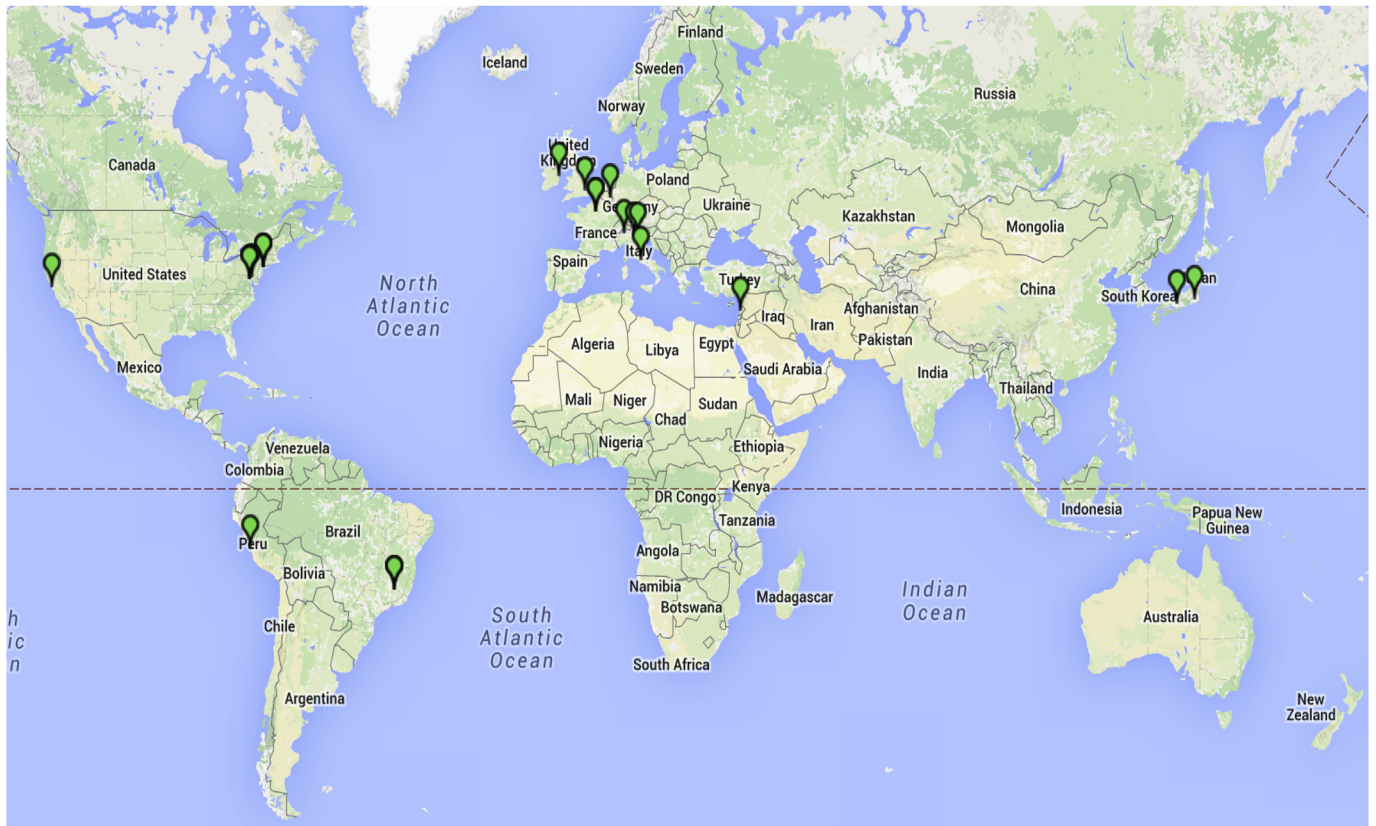


Fig. 1. The global reach of the HTLV taskforce.

Table 1
Members of the GVN taskforce on HTLV-1.

Members	Home Institution	Email address
Accolla, Roberto	University of Insubria, Varese, Italy	accolla.roberto@gmail.com
Bangham, Charles	Imperial College, London, UK	c.bangham@imperial.ac.uk
Bazarbachi, Ali	American University of Beirut, Beirut, Lebanon	bazarbac@aub.edu.lb
Bertazzoni, Umberto	University of Verona, Verona, Italy	umberto.bertazzoni@univr.it
Carneiro-Proietti, Anna Barbara de Freitas	Fundação Hemominas, Belo Horizonte, Brasil	annaproietti@gmail.com
Cheng, Hua	Institute of Human Virology, Baltimore, USA	HCheng@ihv.umaryland.edu
Chieco-Bianchi, Luigi	University of Padova, Padova, Italy	luigi.chiecobianchi@unipd.it
Ciminale, Vincenzo	University of Padova, Padova, Italy	v.ciminale@unipd.it
Coelho-dos-Reis, Jordana	René Rachou Research Center, FIOCRUZ, Belo Horizonte, Brazil	jordana.reis@cpqrr.fiocruz.br
Esparza, José	Institute of Human Virology, Baltimore, USA	jose.esparza5@live.com
Gallo, Robert C.	Institute of Human Virology, Baltimore, USA	rgallo@ihv.umaryland.edu
Gessain, Antoine	Institut Pasteur, Paris, France	antoine.gessain@pasteur.fr
Gotuzzo, Eduardo	Tropical Medical Institute Alexander von Humboldt, Lima, Peru	egh@upch.edu.pe
Hall, William	Center for Research in Infectious Disease, Dublin, Ireland	william.hall@ucd.ie
Harford, Joseph	National Cancer Institute, NIH, Bethesda, USA	joe.harford@nih.gov
Hasegawa, Hideki	National Institute of Infectious Diseases, Tokyo, Japan	hasegawa@nih.go.jp
Hermine, Olivier	Hôpital Necker, Paris, France	olivier.hermine@fondationimagine.org
Jacobson, Steven	National Institute of Neurological Disorders and Stroke, NIH, Bethesda, USA	steven.jacobson@nih.gov
Macchi, Beatrice	University of Rome Tor Vergata, Rome, Italy	macchi@med.uniroma2.it
Macpherson, Calum	St. George's University, Grenada, West Indies	cmacpherson@sgu.edu
Mahieux, Renaud	Ecole Normale Supérieure de Lyon, Lyon, France	renaud.mahieux@ens-lyon.fr
Matsuoka, Masao	Kyoto University, Kyoto, Japan	mmatsuok@virus.kyoto-u.ac.jp
Murphy, Edward	University of California, San Francisco, USA	murphy@ucsf.edu
Peloponese, Jean-Marie	University of Montpellier, Montpellier, France	jean-marie.peloponese@univ-montp1.fr
Simon, Viviana	Icahn School of Medicine at Mount Sinai, New York, USA	viviana.simon@mssm.edu
Tagaya, Yutaka	Institute of Human Virology, Baltimore, USA	ytagaya@ihv.umaryland.edu
Taylor, Graham P	Imperial College London, London, UK	g.p.taylor@imperial.ac.uk
Watanabe, Toshiki	University of Tokyo, Tokyo, Japan	tnabe@ims.u-tokyo.ac.jp
Willems, Luc	University of Liege, Belgium	luc.willems@ulg.ac.be
Yamano, Yoshihisa	St. Marianna University School of Medicine, Kanagawa, Japan	yyamano@marianna-u.ac.jp

et al., 2016).

Diagnosis of HTLV-1 infection is based on ELISA, which is unable to distinguish HTLV-1 from HTLV-2 and, therefore, requires confirmation by immunoblot and PCR, two techniques that are not convenient for routine screening. As a consequence, HTLV-1 prevalence in almost half of the world is unknown (Fig. 2). The current figure of 5–10 million HTLV-1-infected individuals is likely to be an underestimate by at least 2-fold (Gessain and Cassar, 2012). Even in high-income countries with a low prevalence of HTLV-1 infection, there is debate about the cost-effectiveness of universal HTLV-1 screening. The low rate of disease onset in infected individuals (below 10%) further disfavors systematic diagnosis of HTLV-1. Identification of HTLV-1 carriers is nevertheless important to avoid transmission through breast-feeding, blood transfusion and sexual intercourse.

In this context, the taskforce promotes the following actions:

- advocate HTLV-1 and HTLV-2 diagnosis, to avoid transmission through breast feeding or organ transplantation;
- understand and quantify zoonotic transmission;
- identify and characterize HTLV-related strains and related species (e.g. HTLV-2, -3 and -4);
- develop a method to reduce mother-to-child transmission through breast feeding in low-income regions with limited access to clean water (e.g. in Northern Argentina, Bolivia, Peru and Brazil);
- provide information about practices and policies that reduce exposure to further risk.

These measures are important to design and set up healthcare management strategies aiming at reducing HTLV-1 prevalence. There is also a potential threat associated with the emergence of hyperpathogenic strains, as described in related viruses (de Brogniez et al., 2015).

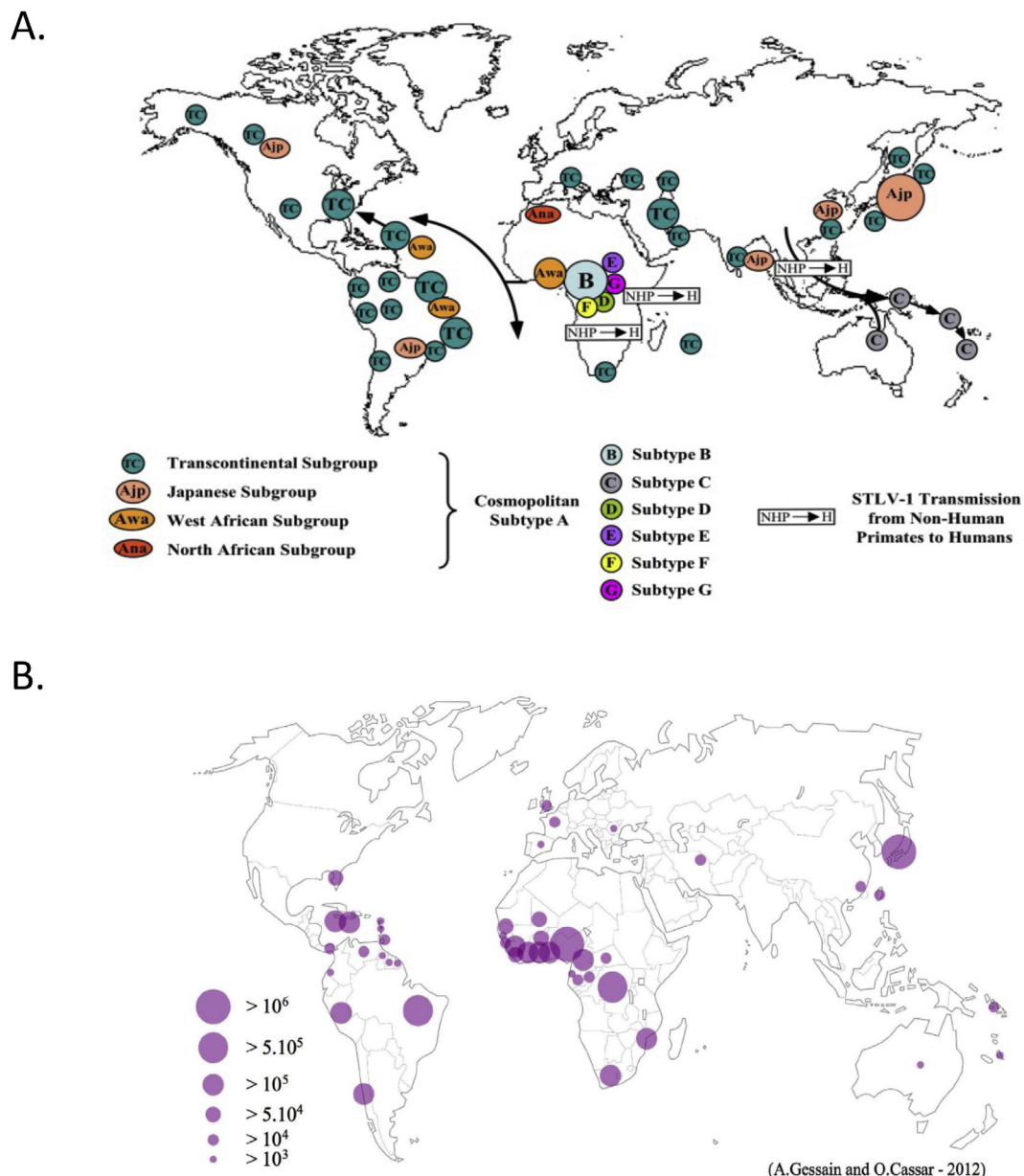


Fig. 2. Geographical distribution of HTLV-1 subtypes (A–G). NHP (non-human primate), H (human). From reference (Gessain and Cassar, 2012).

3.2. Identify biomarkers to predict disease progression

Besides ATL and HAM/TSP, persistent infection by HTLV-1 also leads to a broad spectrum of diseases associated with significant morbidity: uveitis, infective dermatitis, crusted scabies, inflammatory rheumatic conditions (rheumatoid arthritis and Sjögren's syndrome), peripheral neuropathies and muscle inflammation (myositis) (Gonçalves et al., 2010). The mechanisms leading to any of these conditions are currently unknown. Since only a minority of HTLV-1 infected subjects will develop symptoms within their life-span, it is essential to predict disease onset and identify patients at risk. Although the genetic background, host determinants and parasitic infections (e.g. *Strongyloides stercoralis*) are associated with a higher probability of developing ATL and HAM-TSP, there is no biomarker able to predict future disease onset at the individual level (Gabet et al., 2000).

In this context, members of the HTLV taskforce propose to:

- further develop whole-genome sequencing to identify host-associated driver mutations in all conditions, as recently performed for ATL (Kataoka et al., 2015);
- correlate the emergence of driver mutations with disease onset;
- develop assays allowing early prediction of differential disease development and the identification of progression.

The availability of these biomarkers will be particularly useful for clinicians facing decision issues of “watch and wait” or treat. A key example is early treatment of chronic ATL that may increase overall survival (Tsukasaki et al., 2009).

3.3. Develop preventive and therapeutic vaccines

In principle, there is no major issue that would impair the development of a conventional preventive vaccine for HTLV-1:

- HTLV-1 infection elicits vigorous humoral and cytotoxic responses that restrict viral replication,
- subunit antigens are immunogenic and protect from infection,
- purified recombinant antigens can easily be produced by conventional methods, and
- worldwide genetic variation of the viral sequence is very limited (Gessain and Cassar, 2012).

Unfortunately, no vaccine is currently available, likely due to the low interest of pharmaceutical companies associated in the restricted markets in industrialized countries. In fact, vaccination would mainly aim to prevent transmission from mother to child and between sexual partners. Even in Japan, where 1 million HTLV-1 carriers are potential transmitters, until very recently the only recommended measure was avoiding of breast-feeding.

Besides prevention, there is also an urgent need for a therapeutic vaccine. Impaired immunity is a major bottleneck limiting the efficacy of currently available treatments of ATL. The proof of principle demonstrating that an immune boost has therapeutic value has been reported (Suehiro et al., 2015). A consortium of clinicians of the HTLV-1 taskforce and a private company is currently exploiting this opportunity (Abstract 4010 Development of an Anti-HTLV-1 Vaccine for the Treatment of Adult T-Cell Leukemia/Lymphoma, 5th ASH meeting, Orlando 2015). Other recommended actions are:

- understand the mechanisms of innate and acquired anti-HTLV immunity, response to vaccines (Gutiérrez et al., 2014) and immune escape of infected T cells;

- promote applied research on vaccines at national and international levels;
- advocate the usefulness of a vaccine for improving public health;
- contact and involve private charitable organizations for support.

3.4. Screen for existing and novel drugs to improve therapy

The treatment of HTLV-1-induced diseases is still unsatisfactory. In fact, there is no standard therapy for ATL, but rather a series of recommendations that differ among countries. First-line treatment of acute ATL and lymphoma can be based on various types of combined chemotherapy: CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone), VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisone), AMP (doxorubicin, ranimustine, and prednisone) or VECP (vindesine, etoposide, carboplatin, and prednisone) (Tsukasaki and Tobinai, 2014). The use of combined chemotherapy is justified by an efficient primary response and by the urgency of treating patients who frequently present in extremely poor condition. Unfortunately, relapse almost invariably occurs due to emergence of p53-mutated chemoresistant leukemic cells, leading to poor survival rates (20% overall survival at 5 years) (Bazarbachi et al., 2010). In most European countries, the USA, the French West Indies and many South American countries, the first-line therapy of aggressive ATL subtypes is either antiviral therapy alone or a combination of antivirals with chemotherapy. The combination of AZT and IFN yields better outcomes (46% overall survival at 5 years), but has some drawbacks, as it requires long-term treatment without interruption resulting in patients' low adherence due to side-effects and treatment fatigue. However, once complete remission has been achieved, doses can be reduced, resulting in better tolerance.

Besides chemotherapy, allogeneic hematopoietic stem cell transplantation (HSCT), with or without a reduced-intensity conditioning regimen, provides an option to treat ATL. Although HSCT has intrinsic risks (graft-versus-host disease, 3-year overall survival rates of approximately 30%) the main advantage is the potential to yield long-term remissions (Kato and Akashi, 2015).

As far as HAM/TSP treatment, most of the present therapeutic approaches aim to reduce the viral load by anti-retrovirals or by tackling the inflammatory state associated with disease with steroids or with steroid-sparing immunosuppressive drugs. However, at present there is no clearly satisfactory and statistically validated treatment for this disease, a situation leading often to progressive loss of motor function and death from respiratory tract infection (Martin et al., 2014).

In this context, a main goal of the HTLV taskforce will be to identify therapies for ATL and HAM/TSP by:

- performing translational research with drugs no longer under patent protection (e.g. valproic acid or arsenic trioxide) (Khour et al., 2013; Olindo et al., 2011);
- collaborating with industrial partners to investigate the off-label use of newly developed agents used in HTLV-1-negative T-cell lymphoma (e.g. anti-CCR4 and anti-CD30). In particular, Mogamulizumab, a humanized anti-CCR4 monoclonal antibody, leads to higher remission rates (mostly in leukemic forms) and prolonged survival in ATL patients.
- investigating synergistic combinations between chemotherapy/HSTC and therapeutic vaccines (Tax peptides, HBZ), including immune therapy targeting immune checkpoint;
- developing consolidation treatments to achieve long-term full remission;

- undertaking research on the mechanisms of chemoresistance and on the biology of cancer stem cells;
- identifying a therapy for HAM/TSP, since currently available treatments are mainly symptomatic;
- broadening international collaboration to develop concerted actions in multiple centers and standardization.

At present, major bottlenecks that impair the development of efficient therapies against HTLV-1-induced diseases are the time, complexity and costs of organizing clinical trials, as well as the limited interest of pharmaceutical companies. Except for Japan, cases are relatively rare in those developed countries capable of developing novel therapies. On the other hand, poor countries with high HTLV-1 prevalence lack funding.

3.5. Perform basic research to unravel mechanisms of viral persistence, replication and pathogenesis to open insights into novel treatments

The mechanism of HTLV-1 infection is a fascinating model to understand the interplay between a small pathogen (less than 10 kb) that interacts with the host and redirects cell fate in favor of its persistence. Since the discovery of HTLV-1, major achievements by members of the HTLV-1 taskforce and others have been reported. These important milestones include the characterization of:

- genes promoting viral replication and persistence (Tax and HBZ) (Matsuoka and Jeang, 2007);

- modes of viral entry and replication (infectious and mitotic cycles) (Ghez et al., 2010; Boxus et al., 2012; Gillet et al., 2011, 2013; Sibon et al., 2006);
- genomic and epigenetic mechanisms leading to ATL (oncogenic stress, driver mutations) (Kataoka et al., 2015; Yamagishi et al., 2012);
- the role of the immune response in the control of infection (Asquith and Bangham, 2008);
- the pathogenic potential of HTLV-2, -3 and -4 (Calattini et al., 2006).

4. Conclusion and perspectives

Since its discovery, the characterization of HTLV-1 has allowed major breakthroughs not only in virology but also in broader fields such as cell signaling and immunology. Unfortunately, this knowledge has insufficiently been translated into the efficient treatment of HTLV-1-induced diseases. Further progress will require both a better understanding of the mechanisms involved in viral persistence and pathogenesis as well as the translation of laboratory discoveries into preventive and therapeutic strategies.

Future goals for research and action are summarized in Fig. 3, and will include:

- systematic screening of HTLV-1-infected individuals to reduce transmission;
- identification of biomarkers to predict disease progression and to target personalized therapy;
- development of vaccines and efficient therapies.

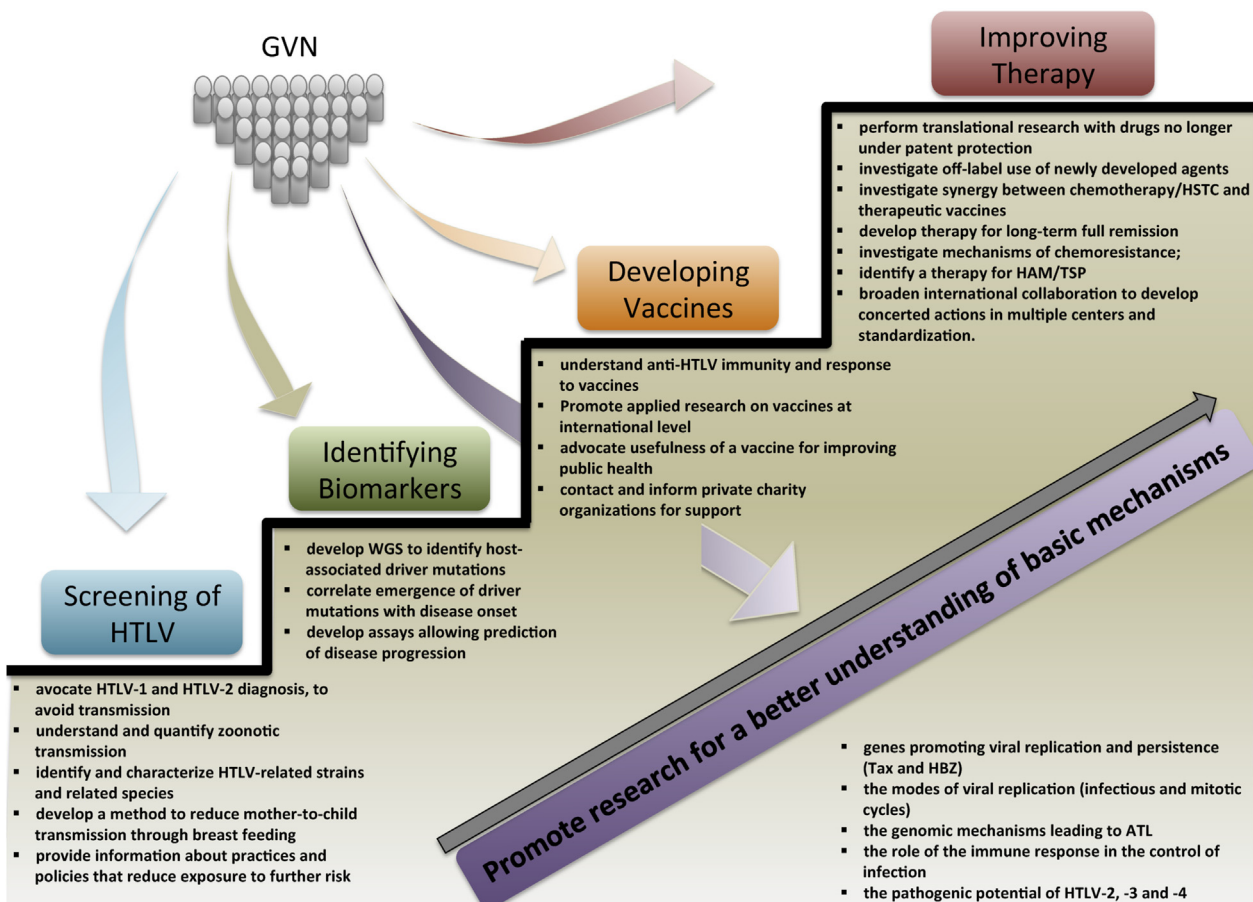


Fig. 3. Goals of the GVN taskforce.

These goals will be achieved, providing that public health authorities support fundamental research and that pharmaceutical industries have an economic interest to develop new therapies. Due to restrictions in publicly-funded research, several qualified research teams lack sufficient funds, have been forced to redirect their research or even quit the field of basic science. Fortunately, the majority still continues to work on a virus that is not prioritized. In this context, the HTLV taskforce will:

- support international collaborative research via training opportunities;
- provide technical support and recommendations to health organizations;
- serve as expert spokespersons and advocates for more research and better treatments.

These tasks fit the overall mission of the GVN, which is designed to combat current viral causes of human disease.

Acknowledgements

We thank Natalia Mercer for manuscript preparation. This work received financial support of the “Fonds National de la Recherche Scientifique” (FNRS), the Télévie, the Interuniversity Attraction Poles (IAP) Program “Virus-host interplay at the early phases of infection” BELVIR initiated by the Belgian Science Policy Office, the Belgian Foundation against Cancer (FBC), the “Centre anticancéreux près ULg” (CAC) and the “Fonds Léon Fredericq” (FLF), the “AgricultureLife” project of Gembloux Agrobiotech (GxABT), the “ULg Fonds Spéciaux pour la Recherche” and the “Plan Cancer” of the “Service Public Fédéral”.

References

- Asquith, B., Bangham, C.R.M., 2008. How does HTLV-I persist despite a strong cell-mediated immune response? *Trends Immunol.* 29, 4–11. <http://dx.doi.org/10.1016/j.it.2007.09.006>.
- Bangham, C.R.M., Araujo, A., Yamano, Y., Taylor, G.P., 2015. HTLV-1-associated myelopathy/tropical spastic paraparesis. *Nat. Rev. Dis. Prim.* 1, 15012. <http://dx.doi.org/10.1038/nrdp.2015.12>.
- Bazarbachi, A., Plumelle, Y., Ramos, J.C., Tortevoeye, P., Otrrock, Z., Taylor, G., Gessain, A., Harrington, W., Panelatti, G., Hermine, O., 2010. Meta-analysis on the use of zidovudine and interferon- α in adult T-cell leukemia/lymphoma showing improved survival in the leukemic subtypes. *J. Clin. Oncol.* 28, 4177–4183. <http://dx.doi.org/10.1200/JCO.2010.28.0669>.
- Boxus, M., Twizere, J.C., Legros, S., Kettmann, R., Willems, L., 2012. Interaction of HTLV-1 Tax with minichromosome maintenance proteins accelerates the replication timing program. *Blood* 119, 151–160. <http://dx.doi.org/10.1182/blood-2011-05-356790>.
- Calattini, S., Chevalier, S.A., Duprez, R., Afonso, P., Froment, A., Gessain, A., Mahieux, R., 2006. Human T-cell lymphotropic virus type 3: complete nucleotide sequence and characterization of the human tax3 protein. *J. Virol.* 80, 9876–9888. <http://dx.doi.org/10.1128/JVI.00799-06>.
- de Brogniez, A., Bouzar, A.B., Jacques, J.-R., Cosse, J.-P., Gillet, N., Callebaut, I., Reichert, M., Willems, L., 2015. Mutation of a single envelope N-linked glycosylation site enhances the pathogenicity of bovine leukemia virus. *J. Virol.* 89, 8945–8956. <http://dx.doi.org/10.1128/JVI.00261-15>.
- Enose-Akahata, Y., Caruso, B., Haner, B., Charlip, E., Nair, G., Massoud, R., Billioux, B.J., Ohayon, J., Switzer, W.M., Jacobson, S., 2016. Development of neurologic diseases in a patient with primate T lymphotropic virus type 1 (PTLV-1). *Retrovirology* 13, 56. <http://dx.doi.org/10.1186/s12977-016-0290-9>.
- Filippone, C., Betsem, E., Tortevoeye, P., Cassar, O., Bassot, S., Froment, A., Fontanet, A., Gessain, A., 2015. A severe bite from a nonhuman primate is a major risk factor for HTLV-1 infection in hunters from central Africa. *Clin. Infect. Dis.* 1–10. <http://dx.doi.org/10.1093/cid/civ145>.
- Gabet, A.-S., Mortreux, F., Talarmin, A., Plumelle, Y., Leclercq, I., Leroy, A., Gessain, A., Clity, E., Joubert, M., Wattel, E., 2000. High circulating proviral load with oligoclonal expansion of HTLV-1 bearing T cells in HTLV-1 carriers with strongyloidiasis. *Oncogene* 19, 4954–4960. <http://dx.doi.org/10.1038/sj.onc.1203870>.
- Gessain, A., Cassar, O., 2012. Epidemiological aspects and world distribution of HTLV-1 infection. *Front. Microbiol.* 3, 1–23. <http://dx.doi.org/10.3389/fmicb.2012.00388>.
- Ghez, D., Lepelletier, Y., Jones, K.S., Pique, C., Hermine, O., 2010. Current concepts regarding the HTLV-1 receptor complex. *Retrovirology* 7, 99. <http://dx.doi.org/10.1186/1742-4690-7-99>.
- Gillet, N.A., Malani, N., Melamed, A., Gormley, N., Carter, R., Bentley, D., Bushman, F.D., Taylor, G.P., Bangham, C.R.M., De, W., Berry, C., 2011. The host genomic environment of the provirus determines the abundance of HTLV-1 – infected T-cell clones. *Blood* 117, 3113–3122. <http://dx.doi.org/10.1182/blood-2010-10-312926>.
- Gillet, N.A., Gutiérrez, G., Rodríguez, S.M., de Brogniez, A., Renotte, N., Alvarez, I., Trono, K., Willems, L., 2013. Massive depletion of bovine leukemia virus proviral clones located in genomic transcriptionally active sites during primary infection. *PLoS Pathog.* 9, e1003687. <http://dx.doi.org/10.1371/journal.ppat.1003687>.
- Gonçalves, D.U., Proietti, F.A., Ribas, J.G.R., Araujo, M.G., Pinheiro, S.R., Guedes, A.C., Carneiro-Proietti, A.B.F., 2010. Epidemiology, treatment, and prevention of human T-cell leukemia virus type 1-associated diseases. *Clin. Microbiol. Rev.* 23, 577–589. <http://dx.doi.org/10.1128/CMR.00063-09>.
- Gutiérrez, G., Rodríguez, S.M., De Brogniez, A., Gillet, N., Golime, R., Burny, A., Jaworski, J.P., Alvarez, I., Vagnoni, L., Trono, K., Willems, L., 2014. Vaccination against δ -retroviruses: the bovine leukemia virus paradigm. *Viruses* 6, 2416–2427. <http://dx.doi.org/10.3390/v6062416>.
- Kataoka, K., Nagata, Y., Kitanaka, A., Shiraishi, Y., Shimamura, T., Yasunaga, J., Totoki, Y., Chiba, K., Sato-Otsubo, A., Nagae, G., Ishii, R., Muto, S., Kotani, S., Watatani, Y., Takeda, J., Sanada, M., Tanaka, H., Suzuki, H., Sato, Y., Shiozawa, Y., Yoshizato, T., Yoshida, K., Makishima, H., Iwanaga, M., Ma, G., Nosaka, K., Hishizawa, M., Itonaga, H., Imaizumi, Y., Munakata, W., Ogasawara, H., Sato, T., Sasai, K., Muramoto, K., Penova, M., Kawaguchi, T., Nakamura, H., Hama, N., Shide, K., Kubuki, Y., Hidaka, T., Kameda, T., Nakamaki, T., Ishiyama, K., Miyawaki, S., Yoon, S.-S., Tobinai, K., Miyazaki, Y., Takaori-Kondo, A., Matsuda, F., Takeuchi, K., Nureki, O., Aburatani, H., Watanabe, T., Shibata, T., Matsuoka, M., Miyano, S., Shimoda, K., Ogawa, S., 2015. Integrated molecular analysis of adult T cell leukemia/lymphoma. *Nat. Genet.* <http://dx.doi.org/10.1038/ng.3415>.
- Kato, K., Akashi, K., 2015. Recent advances in therapeutic approaches for adult T-cell leukemia/lymphoma. *Viruses* 7, 6604–6612. <http://dx.doi.org/10.3390/v7122960>.
- Khour, G., Rezaee, R., Farid, R., Ghantous, A., Rafatpanah, H., Tarhini, M., Kooshyar, M.M., El Hajj, H., Berry, F., Mortada, M., Nasser, R., Shirdel, A., Dassouki, Z., Ezzedine, M., Rahimi, H., Ghavamzadeh, A., de The, H., Hermine, O., Mahmoudi, M., Bazarbachi, A., 2013. The combination of arsenic, interferon- α , and zidovudine restores an “immunocompetent-like” cytokine expression profile in patients with adult T-cell leukemia lymphoma. *Retrovirology* 10, 91. <http://dx.doi.org/10.1186/1742-4690-10-91>.
- Martin, F., Taylor, G.P., Jacobson, S., 2014. Inflammatory manifestations of HTLV-1 and their therapeutic options. *Expert Rev. Clin. Immunol.* 10, 1531–1546. <http://dx.doi.org/10.1586/1744666X.2014.966690>.
- Matsuoka, M., Jeang, K.-T., 2007. Human T-cell leukaemia virus type 1 (HTLV-1) infectivity and cellular transformation. *Nat. Rev. Cancer* 7, 270–280. <http://dx.doi.org/10.1038/nrc2111>.
- McSweeney, E., Weaver, S.C., Lecuit, M., Frieman, M., Morrison, T.E., Hrynkow, S., 2015. The global virus Network: challenging chikungunya. *Antivir. Res.* 120, 147–152. <http://dx.doi.org/10.1016/j.antiviral.2015.06.003>.
- Murphy, E.L., 2016. Infection with human T-lymphotropic virus types-1 and -2 (HTLV-1 and -2): implications for blood transfusion safety. *Transfus. Clin. Biol. J. Société Fr. Transfus. Sang.* 23, 13–19. <http://dx.doi.org/10.1016/j.tracli.2015.12.001>.
- Olindo, S., Belrose, G., Gillet, N., Rodríguez, S., Boxus, M., Verlaeten, O., Asquith, B., Bangham, C., Signate, A., Smadja, D., Lezin, A., Cesaire, R., Willems, L., 2011. Brief report Safety of long-term treatment of HAM/TSP patients with valproic acid. *Blood* 118, 6306–6309. <http://dx.doi.org/10.1182/blood-2011-04-349910>.
- Pique, C., Jones, K.S., 2012. Pathways of cell-cell transmission of HTLV-1. *Front. Microbiol.* 3, 1–14. <http://dx.doi.org/10.3389/fmicb.2012.00378>.
- Richard, L., Mouinga-Ondémé, A., Betsem, E., Filippone, C., Nerrienet, E., Kazanji, M., Gessain, A., 2016. Zoonotic transmission of two new strains of human T-lymphotropic virus type 4 in hunters bitten by a Gorilla in central Africa. *Clin. Infect. Dis.* 1–4. <http://dx.doi.org/10.1093/cid/ciw389> ahead of p.
- Sibon, D., Gabet, A.S., Zandecki, M., Pinatel, C., Thète, J., Delfau-Larue, M.H., Rabaoui, S., Gessain, A., Gout, O., Jacobson, S., Mortreux, F., Wattel, E., 2006. HTLV-1 propels untransformed CD4+ lymphocytes into the cell cycle while protecting CD8+ cells from death. *J. Clin. Investig.* 116, 974–983. <http://dx.doi.org/10.1172/JCI27198>.
- Suehiro, Y., Hasegawa, A., Iino, T., Sasada, A., Watanabe, N., Matsuoka, M., Takamori, A., Tanosaki, R., Utsunomiya, A., Choi, I., Fukuda, T., Miura, O., Takaishi, T., Teshima, T., Akashi, K., Kannagi, M., Uike, N., Okamura, J., 2015. Clinical outcomes of a novel therapeutic vaccine with Tax peptide-pulsed dendritic cells for adult T cell leukaemia/lymphoma in a pilot study. *Br. J. Haematol.* 169, 356–367. <http://dx.doi.org/10.1111/bjh.13302>.
- Tsukasaki, K., Hermine, O., Bazarbachi, A., Ratner, L., Ramos, J.C., Harrington, W., O'Mahony, D., Janik, J.E., Bittencourt, A.L., Taylor, G.P., Yamaguchi, K., Utsunomiya, A., Tobinai, K., Watanabe, T., 2009. Definition, prognostic factors, treatment, and response criteria of adult T-cell leukemia-lymphoma: a proposal from an international consensus meeting. *J. Clin. Oncol.* 27, 453–459. <http://dx.doi.org/10.1200/JCO.2008.18.2428>.
- Tsukasaki, K., Tobinai, K., 2014. Human T-cell lymphotropic virus type I-associated adult T-cell leukemia-lymphoma: new directions in clinical research. *Clin.*

Cancer Res. 20, 5217–5225. <http://dx.doi.org/10.1158/1078-0432.CCR-14-0572>.
Yamagishi, M., Nakano, K., Miyake, A., Yamochi, T., Kagami, Y., Tsutsumi, A.,
Matsuda, Y., Sato-Otsubo, A., Muto, S., Utsunomiya, A., Yamaguchi, K.,

Uchimaru, K., Ogawa, S., Watanabe, T., 2012. Polycomb-mediated loss of miR-31
activates nik-dependent NF- κ B pathway in adult T cell leukemia and other
cancers. *Cancer Cell* 21, 121–135. <http://dx.doi.org/10.1016/j.ccr.2011.12.015>.