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IS THERE A CAUSAL RELATION BETWEEN RADIO FREQUENCY EMISSIONS AND AIDS ?

Vincent Lauer*

Abstract: It is shown that pathogens likely to be advantaged by radio frequency electromagnetic fields at low power use self-mimicry and antigen variation. Amongst these pathogens, HIV (and its animal counterparts) is the sole virus which can potentially evade the immune system, because due to its inherent capability to suppress the humoral immune system it only needs its epitopes to be non-recognizable after restriction by MHC class I , whilst other viruses must yield epitopes which are non-recognizable both after restriction by MHC classes I and II. The biological mechanisms of AIDS, its relation with related diseases in other mammals, and its early history, are shown to be consistent with the hypothesis of a causal relation between AIDS and radiofrequency electromagnetic waves. Further, this hypothesis makes it possible to propose several scenarios for the emergence of HIV/SIV. According to a preferred and consistent scenario, HTLV-1/STLV-1 would have evolved towards HIV/SIV due to an impaired immune system response against the virus due to exposure to electromagnetic waves. This evolution would have been accelerated by cross-species transmissions to and from non-human primates and by genetic diversity within the human species. It is concluded that there is good support for the hypothesis that AIDS was caused by exposure to electromagnetic waves, that this hypothesis can be tested, and that if this hypothesis is correct it would make it possible to eradicate AIDS.

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1 Introduction.

It was shown in (Lauer 2013, 2014 a,b, 2015) that electromagnetic fields interact with the immune system, including at very low power. A pro-pathogen effect of electromagnetic fields in cases of permanent exposure is expected, and such effect can potentially occur at extremely low power for self-mimicking pathogens.

Thus, the possible existence of pro-pathogen effects at extremely low power has been mentioned but not yet confirmed. In the present paper, I first determine on a theoretical basis the essential characteristics of pathogens expected to react to electromagnetic waves at low power. Amongst these pathogens, HIV is shown to be the only one with a potential capacity to entirely evade the immune system. The biological mechanisms of AIDS and its history are shown to be consistent with a causal effect of permanent electromagnetic waves on AIDS. These findings thus substantiate the hypothesis that there is a causal effect between permanent exposure to electromagnetic waves and AIDS.

The present paper deals, amongst other, with the origins of AIDS. This question has been widely debated. The mainstream opinion is that transfer from non-human primates to humans occurred several times during the 20th century and that some environmental factors caused this transfer to be successful and yield the AIDS epidemic, which had not been the case in the previous tens of thousands of years during which modern humans were in contact with non-human primates. This approach may be correct; however it fails to identify the environmental factor, which is an essential issue. Hypotheses as to the environmental factor are numerous; it has for example been said that bushmeat from apes and monkeys was scarce before guns became widely available; other popular theories include “contaminated needles”, “sexual liberation” or “conspiracy”. Whilst these theories may conceivably explain why HIV/AIDS occurred, none of them really answers the question of why HIV/AIDS did not occur earlier, nor lends itself to any validation test. The present paper brings a fundamentally new proposal as to the environmental factor, and proposes consistent scenarios for the emergence of immunodeficiency viruses and diseases.

Readers are advised to use (Lauer 2014b), which describes the general interaction of electromagnetic waves with the immune system, as a reference for understanding the present paper. Like was the case in previous papers with regards to the interaction of electromagnetic waves with the immune system, the present paper can be said to develop a “model” of AIDS. Efforts have been made to deal with most essential aspects of established knowledge related to immunodeficiency viruses and diseases. Yet the reader is encouraged to not get lost into details. The present paper proposes a global understanding of why and how AIDS emerged, and will be useful only if readers grasp this global understanding.

2 Self mimicry and Antigenic variation increase pathogen sensitivity to radiofrequency exposure.

2.1 Simple explanation.

The number of epitopes that can be obtained after restriction by MHC class I (or class II) is significantly higher than the number of phenotypically different naïve mature T cells in the body. Therefore, in order to ensure that any non-self epitope can be recognized and eliminated, each T lymphocyte must recognize a relatively large number of epitopes as its "cognate" epitopes. Each T lymphocyte has a high affinity for some epitopes which it recognizes, and a low (but still above the recognition threshold) affinity for other epitopes which it recognizes. Millions of years of evolution yielded a "lymphocyte coverage" of epitopes which is adapted so that substantially all non-self epitopes are recognized. This lymphocyte coverage represents a cost for the organism, and therefore it is not uselessly oversized. Thus, some non-self epitopes are recognized only by lymphocytes that have a positive but low affinity for the epitope.

Exposure to electromagnetic waves decreases the affinity of lymphocytes for epitopes pursuant to the inhibitory mechanism "INH" (Lauer 2014b). In most cases, the affinity remains above a recognition threshold and the epitope remains recognizable. But for weakly recognized epitopes the affinity goes below the recognition threshold, and the epitope is no more recognizable. Such non-recognizable epitope will be said to be in "**protection gaps**" of the lymphocyte cover, in the **discrete space** made up of all possible non-self MHC class I (or MHC class II)-restricted epitopes. Since epitope recognition is naturally less efficient near self epitopes (because negative selection eliminates lymphocytes that recognize self epitopes), these non-recognizable epitopes (or equivalently these protection gaps) tend to be near self epitopes. A pathogen optimized to escape recognition must therefore present epitopes that are near self epitopes (i.e. the pathogen must be self-mimicking), because such epitopes have a higher chance to be amongst the non-recognizable epitopes.

The detailed characteristics of each T lymphocyte is determined by random changes in the hypervariable regions in its TCR during maturation in the bone marrow, so that it is unpredictable and it differs between different individuals. Thus a non-self epitope which in the presence of artificial electromagnetic waves escapes T lymphocyte recognition in one individual will be recognized in another individual. This generally prevents epidemic spreading of a pathogen. To be able to spread epidemically, a pathogen must be able to adapt its MHC-restricted epitopes after entering a new host organism so as to occupy the protection gaps specific to that individual host, i.e. it must be capable of antigenic variation.

Thus, self-mimicking pathogens capable of antigenic variation in the host organism are particularly likely to be favored by electromagnetic waves, because these characteristics are necessary to generate epitopes that can occupy protection gaps made available by radiofrequency exposure, and thus evade recognition by the adaptive immune system of such epitopes – which are restricted by either MHC class I or MHC class II.

Also, self-mimicking pathogens are not easily recognized by the innate immune system, which unlike the adaptive immune system is not capable of fine discrimination between self and non-self, and thus attacks only what is "grossly" non-self. Therefore, if a self-mimicking pathogen evades recognition by the adaptive immune system by antigenic variation in the presence of protection gaps, it essentially evades recognition by the entire immune system.

2.2 Graphic description of protection gaps

Different lymphocytes recognize different numbers of epitopes. A lymphocyte which has a lower value of its Rabi frequency Ω_{ab} in the presence of its cognate epitope (as defined in Lauer 2014b) has a stronger affinity $Log\left(\frac{\Omega_{bc}}{\Omega_{ab}}\right)$ for its cognate epitope. However a low Ω_{ab} implies a more efficient blocking of the (a) to (b) path which based on Figure 4 of (Lauer 2014b) implies a higher specificity, i.e. the lymphocyte recognizes a smaller number of epitopes. Thus higher specificity is associated with higher affinity and vice versa.

Different lymphocytes have different specificities, which has an impact on epitope recognition. In order to understand epitope recognition better, I will use a simplified model in which T lymphocytes are either class 1 corresponding to high specificity and high affinity lymphocytes recognizing a restricted range of epitopes, or class 2 corresponding to low specificity and low affinity lymphocytes recognizing a wider range of epitopes.

Epitopes form a **discrete space** which is uneasy to represent. In order to make a graphic representation possible, I will use a continuous space analogy: I represent different epitopes (or epitopes) as points along an axis x (Figure 1). This representation is not very well-connected to the "real world" and is to be viewed only as an analogy which is useful to support reasoning.

Figure 1 is shown for the non-exposed case. The density of class 1 T lymphocytes is adapted to ensure that, ignoring negative selection, any epitope is recognized by class 1 T lymphocytes with a sufficient affinity corresponding to a protection level PL substantially higher than the non-exposed threshold level TNE corresponding to a separation between recognition and non-recognition of epitopes. However negative selection in the thymus suppresses class 1 T lymphocytes that recognize self epitopes (here SA1) so that self epitopes and a few epitopes around them are not recognized by class 1 T lymphocytes. Ignoring negative selection, Class 2 T lymphocytes ensure a minimal protection level which is higher than PL, but negative selection

suppresses class 2 T lymphocytes that recognizes self epitopes (here SA1). After negative selection, epitope recognition near the self epitope (SA1) is dominantly achieved by class 1 T lymphocytes as is apparent from Figure 1, because of the lower "slope" of the affinity curves of class 2 T lymphocytes. These adaptations of lymphocyte cover result from a long term evolution. Class 2 T lymphocytes optimize the affinity for epitopes which are far from self epitopes. Class 1 T lymphocytes ensure that epitopes which are near to self epitopes are recognized with a minimum affinity PL. If the protection level reached by class 2 T lymphocytes far from self epitopes was to be achieved only by high-specificity class 1 T lymphocytes, the number of required class 1 T lymphocytes would be higher than what the immune system can provide.

Note that the presence or absence of the "limit case" class 2 T lymphocyte LLN does not modify the protection level PL or the affinity AP2N (resp. AP1N) for the non-self epitopes PA2 (resp. PA1).

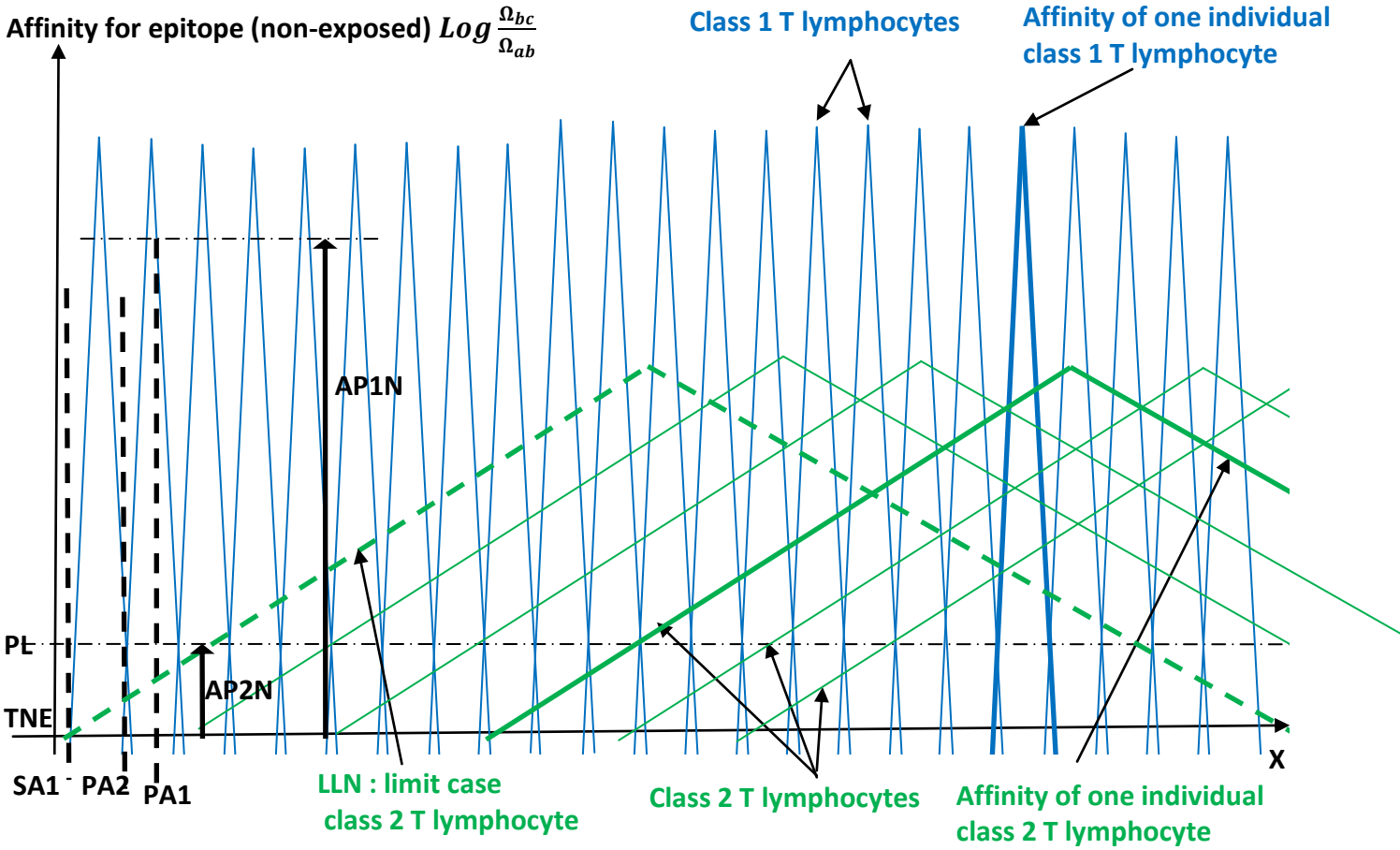

Figure 1: affinity of T lymphocytes for presented epitopes between two self epitopes <u>in non-exposed situation</u>. Horizontal axis is an arbitrary coordinate X. SA1 is the position of a self epitopes on axis X. PA1, PA2 are positions of non-self (pathogen) epitopes (or epitopes) on axis X. TNE (corresponding to the horizontal axis) is the non-exposed threshold level. T lymphocytes having affinity for SA1 which is above TNE are eliminated by negative selection. PL: protection level. Class 1 T lymphocytes are near enough from each other on axis x to ensure that, ignoring negative selection, the affinity is always superior to PL for any epitope. AP1N [resp. AP2N]: affinity (of the strongest binding T lymphocyte) for PA1 [resp.PA2] epitope, relative to the affinity for self epitopes. LLN: most strongly binding class 2 T lymphocyte which can survive negative selection.

In an exposed situation, the threshold TNE is modified to TE as shown on Figure 2, corresponding to the inhibition of epitope recognition by a permanent electromagnetic wave (Lauer 2014b). More T lymphocytes survive negative selection, the supplementary survivors being mostly class 2. In the presence of the limit case class 2 T lymphocyte LLE the affinity AP2E for the epitope PA1 is strongly reduced as compared to the corresponding non-exposed affinity AP2N. If the limit case class 2 T lymphocyte LLE is absent, the affinity becomes negative, i.e. the affinity (AP2EB) for the non-self epitope PA2 becomes less than the affinity for non-self epitopes, which means that the epitope PA2 is not recognized at all. Thus T lymphocytes recognize the non-self epitope PA2 either weakly or not at all, the recognition level being highly dependent on the density of the class 2 T lymphocytes cover and on the coincidence between the self epitope SA1 and the zero affinity of a class 2 T lymphocyte. However the affinity AP1E for non-self epitope PA1, which is high, is un-modified as compared to the exposed case.

Thus exposure to the electromagnetic wave does not modify the recognition of non-self epitope PA1 by T lymphocytes but strongly weakens or even suppresses recognition of non-self epitope PA2.

Unlike PA1, non-self epitope PA2 is in a "**<u>protection gap</u>**", i.e. in the least strongly recognized area between two class 1 T lymphocytes, which in the presence of radiofrequency exposure becomes a very weakly recognized or non-recognized area. The exact affinity curve of each T lymphocyte is determined by random changes in the hypervariable regions in its TCR during

maturation in the bone marrow and is thus unpredictable. Thus a non-self epitope PA2 which escapes T lymphocyte recognition in one individual will be recognized in another individual. This generally prevents epidemic spreading of a pathogen presenting the PA2 epitope.

However, if a pathogen presenting near-self epitopes (PA1) is able to modify its presented epitopes after entering its host organism, it may present a recognized epitope (PA1) when entering the host but later escape the adaptive immune system by presenting a non-recognized epitope (PA2). Such a pathogen may thus survive in different hosts by adapting to the individual protection gaps of each host. It is therefore highly favored by exposure, even though far from the self epitope SA1 the exposure level does not significantly affect epitope recognition, and even though near to the self epitope SA1 a majority of non-self epitopes may still be well-recognized.

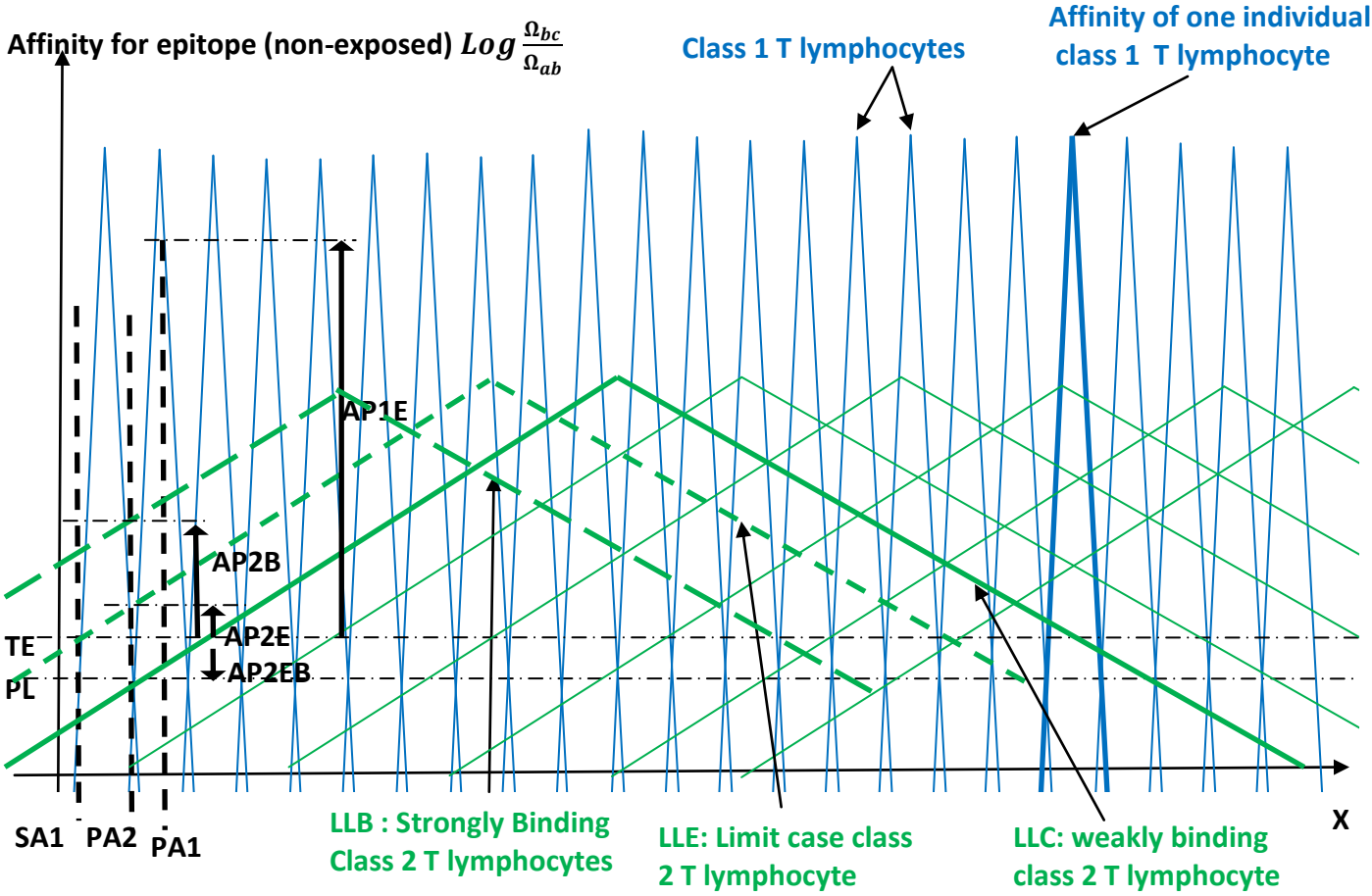

Figure 2: affinity of T lymphocytes for presented epitopes between two self epitopes <u>in exposed situation</u>. Horizontal axis is an arbitrary coordinate X. SA1 is the position of a self epitopes on axis X. PA1, PA2 are positions of non-self (pathogen) epitopes (or epitopes) on axis X. Non-exposed case. TE is the exposed threshold level. T lymphocytes having affinity for SA1 which is above TE are eliminated by negative selection. PL: protection level. Class 1 T lymphocytes are near enough from each other on axis x to ensure that, ignoring negative selection, the affinity is always superior to PL for any epitope. LLE: most strongly binding class 2 T lymphocyte which can normally survive negative selection. LLB: strongly binding T lymphocyte which escaped negative selection but will be eliminated by Treg lymphocytes. AP1E [resp. AP2E]: affinity (of the strongest binding T lymphocyte) for PA1 [resp.PA2] epitope in the presence of LLN, relative to the affinity for self epitopes. AP2B: affinity of LLB for PA2. AP2EB: affinity (of the strongest binding T lymphocyte) for PA2 epitope in the absence of LLN and LLB, relative to the affinity for self epitopes.

3 A pathogen cannot evade both the cellular and humoral immune systems by antigenic variation in the presence of protection gaps.

An antigen restricted by MHC class I [resp. class II] can be said to be in a "protection gap" for restriction bu MHC class I [resp. class II] if all of its MHC-class I [resp. class II] –restricted epitopes are in "protection gaps" of the CD8+ [resp. CD4+} lymphocyte cover. This defines **<u>protection gaps in the discrete space made up of all antigens</u>**, for MHC class I and for MHC class II.

However, protection gaps for antigens restricted by MHC class I are independent of protection gaps of antigens restricted by MHC class II, so they rarely coincide. If an antigen recognized by both the cellular adaptive immune system (corresponding to

MHC class I) and the humoral adaptive immune system (corresponding to MHC class II) is to evade the immune system entirely, it must be both in a protection gap for MHC class I and in a protection gap for MHC class II. Since these protection gaps rarely coincide, an antigen which is recognized by both the cellular and the humoral immune systems cannot easily escape adaptive immunity through antigenic variation in the presence of protection gaps.

For this reason, antigenic variation in the presence of protection gaps allows antigens to escape recognition by the adaptive humoral immune system or by the adaptive cellular immune system, but not by both of them. A self-mimicking pathogen capable of evading the immune system efficiently through antigenic variation in the presence of protection gaps must therefore either be naturally recognized by only one of the adaptive humoral or cellular immune systems, or be able to somehow neutralize one of these immune systems.

4 Candidate pathogens.

Based on section 2 self-mimicking pathogens with a capacity to vary their presented antigens can potentially be favored by electromagnetic waves. This includes some bacterias (Borrelia Burgdorferi, Neisseria, streptococcus, mycoplasma), protozoa (trypanosoma brucei), viruses (Flaviridiae, Hepatite C virus, dengue virus, HIV).

4.1 Viruses: only HIV can entirely escape the adaptive immune system

Viruses can enter host cells and be recognized by the humoral immunity (mediated by CD4+ T lymphocyte –dependent activation of B cells) and by the cellular immunity (i.e. by effector CD8+ T lymphocytes). In particular, surface proteins may activate both the recognition by humoral immunity (when present on host cell surface after entering a host cell or when outside host cells) and the recognition by effector CD8+ T lymphocytes (after entering a host cell). As discussed in section 3, these surface proteins can evade the adaptive humoral immune system or the adaptive cellular immune system, but not both. This is why viruses are ordinarily seen to evade the humoral immune response against their surface (or structural) proteins by antigenic variation (van Dorn et al 1995, Wang et al 2002, Li et al 2005), but the same do not simultaneously evade recognition by effector T lymphocytes of their surface proteins after restriction by the MHC class I system. Ordinary viruses do not have the capacity to entirely evade the immune system.

T lymphocyte dependent activation requires CD4+ T lymphocytes to meet an antigen-presenting cell such as a macrophage or a dendritic cell. However if the antigen-presenting cell presents HIV epitopes, it is also likely to be infected by intact HIV viruses, even at low level. Such HIV viruses can take advantage of the contact between the CD4+ T lymphocyte and the antigen-presenting cell to enter the CD4+ T lymphocyte. Therefore most CD4+ T lymphocytes that are capable of triggering anti-HIV antibody production by B cells are infected by HIV. The same is true for follicular CD4+ helper T lymphocytes that are required to sustain antibody production in germinal centers (Janeway et al 2001). If CD4+ T lymphocytes are not directly infected as described, they may be infected from other CD4+ lymphocytes in lymph nodes or follicles, or otherwise.

If B cells produce antibodies against HIV epitopes that are presented by CD4+ T lymphocytes, they trigger the destruction of these HIV-infected CD4+ T lymphocytes required to sustain antibody production, so that the germinal centers cease to grow or produce antibody. For this reason, in the first stages of the infection the serum of HIV-infected patients does not comprise antibodies that are effective against HIV-infected T lymphocytes (Ruppach et al 2000), although it may comprise antibodies that are effective against other HIV-infected cellular types.

Antibody (A1) production of a B cell line (B1) in its germinal center is thus stopped or slowed down shortly after initiation of the germinal center. Some CD4+ helper T lymphocytes (Th1) still able to sustain antibody production by B1 may survive and the virus inside these lymphocytes can mutate. If the virus inside one Th1 lymphocyte is replaced by a new dominant variant so that the antibodies A1 no more bind its presented epitopes, the resulting Th1b lymphocyte can sustain antibody production by the B1 cells without being neutralized by the antibody A1. Therefore production of antibody A1 in the germinal center resumes, and antibody appears in the sera which is directed against the original version of the virus but not against the new variant. Such antibody production was observed after typically more than one year (Moog et al 1997). This antibody production although existing remains unable to neutralize the new dominant viral variant in CD4+ T lymphocytes and is thus no protection against HIV/AIDS. In short, HIV has an inherent capability to permanently neutralize the humoral immune response against the dominant variant.

Because HIV has this inherent capability to suppress the humoral immune response, it needs only evade recognition by effector T lymphocytes to entirely evade recognition by the immune system. Therefore, a variant of HIV needs only yield non-recognizable epitopes after restriction by MHC class I to escape the immune system entirely, unlike other viruses which need to yield non-recognizable epitopes both after restriction by MHC classes I and II. Therefore, unlike other viruses, HIV has the potential capability to essentially escape the immune system entirely.

Notably, other retroviruses that also infect T lymphocytes (HTLVs) do not have the same capacity because they induce T lymphocyte proliferation (rather than T lymphocyte apoptosis for HIV), which may possibly produce some un-infected helper T lymphocytes able to sustain antibody production by corresponding B cells or alternatively allow T lymphocytes in germinal

centers to replicate faster than they are suppressed by the humoral immune system. Inducing T lymphocyte proliferation rather than T lymphocyte apoptosis is an alternative survival strategy for the pathogen, and is the dominant difference between HTLV and HIV.

HIV thus appears as the sole existing virus which has the theoretical capability to entirely evade the immune response through antigenic variance in the presence of a permanent exposure to a very low power electromagnetic wave. Other viruses may also be affected by exposure to electromagnetic waves pursuant to Table 1 column E of (Lauer 2014b), but at significantly stronger exposure power because they cannot easily present epitopes which fall into protection gaps both after restriction by MHC classes I and II.

In addition, the humoral response against previous HIV variants accelerates eliminations of these variants and their replacement by the dominant variant, and thus favors faster mutation and evolution of the virus.

4.2 Protozoa and bacteria.

Protozoa and most bacteria are suppressed by the humoral adaptive immune system but not by the cellular adaptive immune system, so that unlike most viruses they need not evade simultaneously the humoral and cellular adaptive immune systems. In order to evade the adaptive immune system entirely, antigenic variation needs only provide surface proteins which are non-detectable by CD4+ T lymphocytes after restriction by MHC class II.

At least one protozoa has been unambiguously shown to react to electromagnetic fields. Trypanosoma Equiperdum, which induces 100% deaths in 5 days in mice, causes no deaths when mice are subject to an appropriate electromagnetic field (Pautrizel et al 1966, Berteaud et al 1971). An explanation was proposed in (Lauer 2014a) and is based on a stimulation of antigen recognition by CD4+ T cells, i.e. a phenomena opposite to the inhibition of antigen recognition by electromagnetic waves which is discussed herein. It is unclear whether artificial electromagnetic fields participate significantly in the high ”natural” pathogenicity of Trypanosoma Equiperdum in mice; however, this experimental result shows that Trypanosoma Equiperdum is sensitive to electromagnetic fields, as expected for a protozoa capable of antigenic variance. The high contrast obtained on death rates based on a manipulation of electromagnetic waves is an experimental confirmation that at least in certain cases pathogens capable of antigenic variance are very significantly affected by electromagnetic fields.

In most bacteria and protozoa, self mimicry and antigenic variance are limited to surface proteins that form the primary target for antibodies. These microorganisms evolved in a world without exposure to electromagnetic waves, in the situation of Figure 1 where there are essentially no “protection gaps”. The evolutionary advantage of antigenic variation was mostly to delay the reaction of the immune system by escaping each response of the immune system one after another, rather than finding protection gaps which did not exist. Accordingly, Borrelia Burgdorferi, some other bacteria, and trypanosoma brucei, have a limited number of pre-defined different surface proteins. The limitation in the number of pre-defined surface proteins also limits the capacity of such surface proteins to find protection gaps. Therefore, despite the interesting case of Trypanosoma Equiperdum in mice, bacteria and protozoa are not expected to be as efficient as HIV in finding “protection gaps” and are thus expected to be less sensitive to very low power exposure.

5 A causal relation between AIDS and permanent electromagnetic fields is consistent with known biology of HIV.

In this section I interprete known biological properties of HIV/AIDS within the framework of section 2 and more specifically Figure 2, assuming that AIDS is caused by exposure to electromagnetic waves causing the immune reaction against HIV to be ruled by Figure 2 instead of Figure 1 (i.e. assuming a causal relation between the presence of electromagnetic fields and AIDS).

5.1 Variant HIV epitopes occupy protection gaps.

After entering the host, HIV usually causes a short-term immune reaction, confirming that it can be transmitted in a form which presents recognizable epitopes (antigens) after restriction by the host’s MHC class I system. It has been shown that after entering the host HIV mutates so as to diminish or escape recognition by cytotoxic T lymphocytes (Price 1997), thus confirming that finding protection gaps is an essential mechanism in HIV.

5.2 Suppression /non-suppression by Treg lymphocytes.

5.2.1 Model of Treg lymphocytes.

I will assume that Treg lymphocytes are essentially redundant with negative thymus selection. In line with the model presented in (Lauer 2014b), Treg lymphocytes are thus viewed as antigen presenting cells presenting self epitopes restricted by the MHC class I. If a CD8+ Cytotoxic T Lymphocyte (CTL) recognizes the self epitope(s) presented by a Treg lymphocyte as its

cognate epitope, the CTL is suppressed (i.e. eliminated or at least neutralized). This model is somewhat rough and ignores possible fine regulation systems, but it is sufficient to explain the fundamental observations.

5.2.2 The observation.

Some HLA allele groups (HLA*B27, HLA-B*57) are enriched in Long-Term-Non-Progressor (LNTP) populations. Epitope-specific CD8+ Cytotoxic T Lymphocytes (CTLs) restricted by these protective HLA allele groups (HLA-B*27 and HLA-B*57) are not suppressed by regulator T lymphocytes (Treg) whilst proliferation of epitope-specific CD8+ T lymphocytes restricted by other allele groups is significantly suppressed by Treg lymphocytes (Elahi et al 2012).

5.2.3 Interpretation.

In protective allele groups, the density (or number) of class 2 T lymphocytes is sufficient so that any non-self HIV epitope PA1 or PA2 (see Figure 2) has a corresponding class 2 T lymphocyte which can recognize it and which is near to the theoretical limit case lymphocyte LLE of Figure 2. The affinity of this class 2 T lymphocyte for the non-self HIV epitope PA2 (relative to recognition threshold TE) is positive (AP2E) but its affinity for the self epitope SA1 is null or negative, so that it recognizes PA2 but not SA1. Since it does not recognize the self epitope SA1, it is not suppressed by Treg lymphocytes.

In non-protective allele groups, the density of class 2 T lymphocytes is lower. At least some non-self HIV epitopes PA2 cannot be recognized by a corresponding class 2 lymphocyte near enough from LLE. Instead, the nearest class 2 lymphocytes are LLB and LLC. The affinity of LLC for PA2 or PA3 is negative so that it does not recognize HIV non-self epitopes. The affinity of LLB for PA2 or PA3 is positive (AP2B) so that it recognizes HIV non-self epitopes and generates a useful immune response, however it is suppressed by Treg lymphocytes because it also recognizes the self epitope SA1.

In principle, the lymphocyte LLB should have been eliminated by negative selection and thus should not have generated an immune response at all. However it may have survived negative selection because of the natural imperfections of negative selection and further because of time-varying waves to which the host was exposed. If the host was temporarily exposed to waves stronger than in the laboratory, impaired negative selection as per Figure 1 of (Lauer 2014b) may have allowed survival of LLB T lymphocytes which in the laboratory environment (but not during the high exposure period in vivo) recognize the self epitope SA1.

5.3 Conserved/non-conserved CTL responses.

A protective effect is also associated with conservation of CTL responses which are dominant in early HIV infection (Dinges et al 2010), despite the later appearance of variant epitopes. Thus stronger affinity for the variant epitopes PA2 is associated with conserved CTL responses, i.e. CTL responses which are broad enough to encompass both the initial epitope (PA1) presented at onset of the infection and the variant epitopes (PA2) which appear later (see Figure 2).

When non-self HIV epitope are recognized by LLE-like class 2 lymphocytes, which are not eliminated by Treg lymphocytes and have a broad response (sufficient to recognize both the initial epitope PA2 and the variant epitope PA1) then the immune response is efficient against HIV and is conserved.

When the class 2 T lymphocytes which are nearest to the limit case LLE are LLB or LLC, either these lymphocytes never recognize the non-self HIV epitopes or they recognize the HIV epitopes temporarily and are later eliminated by Treg lymphocytes. Thus protection against HIV is left to class 1 T lymphocytes, which individual response is not broad enough to encompass both the initial epitope (PA1) and the variant epitope (PA2). The CTL response is thus not conserved. Further, protection gaps exist in the class 1 T lymphocyte cover, so that HIV variants finally evolve to yield epitopes that are in protection gaps, thus escaping the immune response.

Thus conserved CTL response is associated with class 2 T lymphocytes and lack of protection gaps, thus efficient immune response, whilst non-conserved CTL response is associated with class 1 T lymphocyte and availability of protection gaps, thus inefficient immune response.

5.4 AIDS is positively [resp. negatively] associated with auto-immunity problems mediated by CD8+ effector T lymphocytes [resp. CD4+ T lymphocyte/B cell association].

AIDS is positively associated with auto-immune problems (Reiter's syndrome, psoriartic arthritis, Sjogren's-like syndrome) but negatively associated with others (systemic Lupus erythematosus SLE) (Zandmann-Goddard 2002). Psoriartic arthritis is dominantly mediated by CD8+ CTLs (Costello 2001, Veale 2005) but SLE is dominantly mediated by the CD4+ T lymphocyte/B cell association (Dörner 2011). Thus it appears that AIDS is positively [resp. negatively] associated with auto-immunity problems mediated by CD8+ effector T lymphocytes [resp. CD4+ T lymphocyte/B cell association].

The positive association with auto-immune problems mediated by CD8+ T lymphocytes is due to the proximity of presented HIV epitopes (PA1, PA2) with self epitopes (SA1) causing T lymphocytes that recognize the presented HIV epitopes to often attack self epitopes (SA1). This occurs with any self-mimicking disease. The negative association with auto-immune diseases

mediated by the CD4+ T lymphocyte/B cell association is a direct consequence of the suppression of the humoral immune response discussed in section 4.

Thus these associations confirm the self-mimicking character of AIDS, which is implied by Figure 1, and the suppression of the humoral immune response.

6 A causal relation between exposure to permanent electromagnetic waves and AIDS is consistent with the early history of AIDS and SIV.

6.1 Weaknesses and inconsistencies of the mainstream theory.

The mainstream theory concerning the emergence of AIDS is that SIVcpzPtt (immune deficiency virus in chimpanzees *Pan troglodytes*), SIVgor (in gorillas), and SIVsmm (in sooty mangabeys) were pre-existing, were transmitted to humans through several cross-species events during the 20th century yielding HIV-1 (from chimpanzees and gorillas) and HIV-2 (from sooty mangabeys), and gave rise to AIDS. SIV itself would have existed for tens of thousands of years (Worobey 2010).

6.1.1 Cross-species transmissions.

According to the mainstream theory, the major epidemic strains of HIV-1 (group M) would have resulted from a cross-species transmission from SIVcpzPtt. This hypothesis that SIV appeared first in chimpanzees and was later transmitted to humans was in part based on the belief that chimpanzees were not affected by an AIDS-like disease and could thus be a natural reservoir of SIV. Thus the finding that wild SIV-infected chimpanzees are affected by an AIDS-like disease (keele 2009, Rudicell 2010) strongly questions the mainstream theory. In particular, an AIDS-like epidemic reached chimpanzees in the Gombe National Park in 2002-2003 (Rudicell 2010), fairly later than the start of the epidemics in humans. It is very surprising to see an epidemic reaching the reservoir host after the host to which the virus was transmitted by a cross-species event, rather than before.

Phylogenetics does not always support the hypothesis of single-directional animal to human transmissions. For example the phylogenetic tree on Figure 4 of (Sharp and Hahn 2011) concerning a region of the viral pol gene suggests that SIVgor and HIV-1 P would both descend from HIV-1 O (i.e. human to animal transmission), whilst at the same time it also suggest that HIV-1 M would descend from SIVcpzPtt (i.e. animal to human transmission).

Only a subset of chimpanzees and gorilla sub-species are affected by SIV (Sharp and Hahn 2011). If SIV had an ancient history in non-human primates, in view of the fact that it affects different species it would be expected to affect all or most sub-species in each affected species.

The non-pathogenic character of SIV in many African primates, as compared to some examples of high pathogenicity in Asian primates, can be viewed as an indication of an ancient co-evolution. However random searches have found several occurrences of HIV in conserved human samples of the Kinshasa area dating back from 1959 and 1960 (Zhu et al 1998, Worobey et al 2008), before the first known case of AIDS in 1963. This shows that HIV was widespread in the Kinshasa area before the appearance of AIDS. This would at first glance imply that a harmless form of HIV preceded the modern pathogenic form, a finding which is further reinforced by molecular clock analysis dating back the emergence of AIDS to the first half of the 20th century. Extending this finding to non-human primates would imply that the relatively harmless character of SIV in many of these primates (as compared to humans) may be an indication of a recent appearance rather than an indication of ancient co-evolution.

Taken as a wgap, the evidence gives little support for the idea of an ancient co-evolution of SIV and non-human primates or to the idea that cross-species transmissions were solely from animals to human, and would rather point to a more complex relationship between HIV and SIVs.

6.1.2 Molecular clock inconsistencies.

Within the mainstream theory, the idea that HIV is younger than SIV is also based on molecular clock analyzes according to which HIV-1 group M appeared early in the 20th century (Worobey et al 2008). A cross-species transmission from non-human primates then appears as the sole reasonable explanation for this sudden emergence, based on the idea that SIV is old and has co-evolved with its hosts.

Also, “fossil” endogenous lentiviruses integrated in the host’s genome (lentiviruses are the family of retroviruses to which HIV/SIV pertain) have been found on several species of mammals (Katzourakis et al 2007, Han and Worobey 2012, …) including primates (Gifford et al 2008), and dated between 7 and 14 millions years. To a certain extent these fossil endogenous lentiviruses substantiate the idea that SIVs may be old.

However the same molecular clock analyzes date SIVs in sooty mangabeys and chimpanzees to 1809 and 1492 respectively (Wertheim and Worobey 2009), and dated the common ancestor of HIV-1, HIV-2 and SIVagm at about 150 years. These dates

are inconsistent with the general idea underlying the mainstream theory, i.e. a co-evolution of primates and SIV. This problem was discussed by several authors but there is no easy answer to this inconsistency (Sharp et al 2000, Holmes 2003).

6.1.3 Why did HIV and AIDS not appear earlier ?

Within the mainstream theory, the question as to why HIV appeared and became pathogenic in the 20th century whilst it had failed to do so in the previous tens of thousands of years during which humans were in contact with presumably infected non-human primates is also left largely un-answered.

Proposed theories comprise the wider availability of bushmeat due to the widespread availability of guns (but this is unlikely to explain the chimpanzee to human cross-species transmission event supposed to have given rise to HIV group M most likely in the 1920s); the "contaminated needle theory"; the "colonialism theory"; the importance of industrialization, sexual liberation, travel, blood industry, the "oral polio vaccine theory". Most of these theories apply to the human species only and thus comfort the idea that the founding event was a cross-species transmission from animal to human which was made possible or successful by an environmental change affecting the recipient species, i.e. humans.

None of these proposed causes explains why absolutely no cross-species transmission event towards humans occurred earlier than the 20th century whilst such cross-species transmission events had occurred earlier between different species of non-human primates that are genetically more distant from each other than humans are from chimpanzees, and which carry SIVs that are more distant from one another than SIVcpzPtt is from HIV-1 group M.

None of these theories explains why HIV became pathogenic in humans and chimpanzees whilst there is evidence that it was originally non-pathogenic.

6.2 The proposed hypothesis resolves the inconsistencies of the mainstream theory.

In this paper, I propose that the adaptive immune system became less efficient during the 20th century, as a consequence of exposure to electromagnetic waves, which prompted the evolution of T-lymphotropic viruses or pre-existing immunodeficiency viruses towards modern immunodeficiency viruses and allowed these modern immunodeficiency viruses to be viable. This approach yields a different view of the mutation rates of these viruses and of their pathogenic capabilities, which largely avoids the inconsistencies of the mainstream theory.

6.2.1 Temporary effects at low to high exposure transitions.

Onset of a new telecommunication network yields a long term loss of efficiency of the immune system against pathogens under permanent exposure conditions as discussed in section 2. Yet under permanent exposure situation, more T lymphocytes survive negative selection in the thymus (Lauer 2014b). But immediately after the low to high exposure transition, these supplementary lymphocytes are not yet present, so that the loss of efficiency is stronger than after stabilization in the permanent exposure conditions. So in addition to the loss of efficiency of the immune system under permanent exposure, there is additionally a transient loss of efficiency of the immune system due to the low to high exposure transition.

In such a transition, non-self epitopes (PA3) which are unusually distant from the self epitope (as is the case in a cross-species transition) suddenly become unrecognized after the transition (Figure 3). This allows foreign "self-mimicking" viruses coming from another species (yielding presented epitope PA3) to not be immediately rejected by the immune system. It takes some time before the immune system generates new class 2 T lymphocytes to "fill the gap" and recognize the PA3 epitope. This transition period leaves time for the foreign self-mimicking virus coming from another species (and presenting epitope PA3 that is unusually far from the self) to progressively mutate in response to a progressively increasing immune pressure as new T lymphocytes are produced by the thymus, so that at the end of the transition period the virus may present epitopes (PA2) that are nearer to the self epitope and thus may be able to survive in the new host under conditions of permanent exposure or even in a non-exposed situation. Depending on the position of the recognition threshold level TET relative to the protection level PL, the strength of both the transient and the permanent effect (after end of the transition period) varies; but during the transition period the effect is always stronger than after stabilization, particularly with regards to viruses that result from a cross-species transmission, so that the transition period is particularly favorable to cross-species transmission events but also to the mutation and emergence of an originally ill-adapted virus.

6.2.2 Mutation rate variability explains inconsistencies in molecular clock dating.

Within the present hypothesis, immunodeficiency viruses have a potential for fast mutations which results from transcription errors; but the limiting factor for mutation speed is likely to be the immune pressure rather than the transcription speed. In the presence of a strong immune pressure before onset of electromagnetic waves, immunodeficiency viruses were either conserved in relatively stable forms capable of surviving in particular hosts, or entirely eliminated. In the present situation, most mutants are likely eliminated by the immune system, with only those which reach a protection gap being able to survive.

When immune pressure is strong, the surviving virus variants tend to yield MHC class I – restricted epitopes that remain in favorable areas in the discrete space of epitopes (see section 2). Such favorable areas must be reasonably invariant amongst different hosts of the same species and are thus expected to be near self epitopes which are widely shared within a species. When immune pressure is low, variants can survive which yield epitopes outside this favorable area, and variants of variants can progressively reach different favorable areas. Thus a period of low immune pressure favors mutation to different favorable areas corresponding to a possibly strong change of genotype.

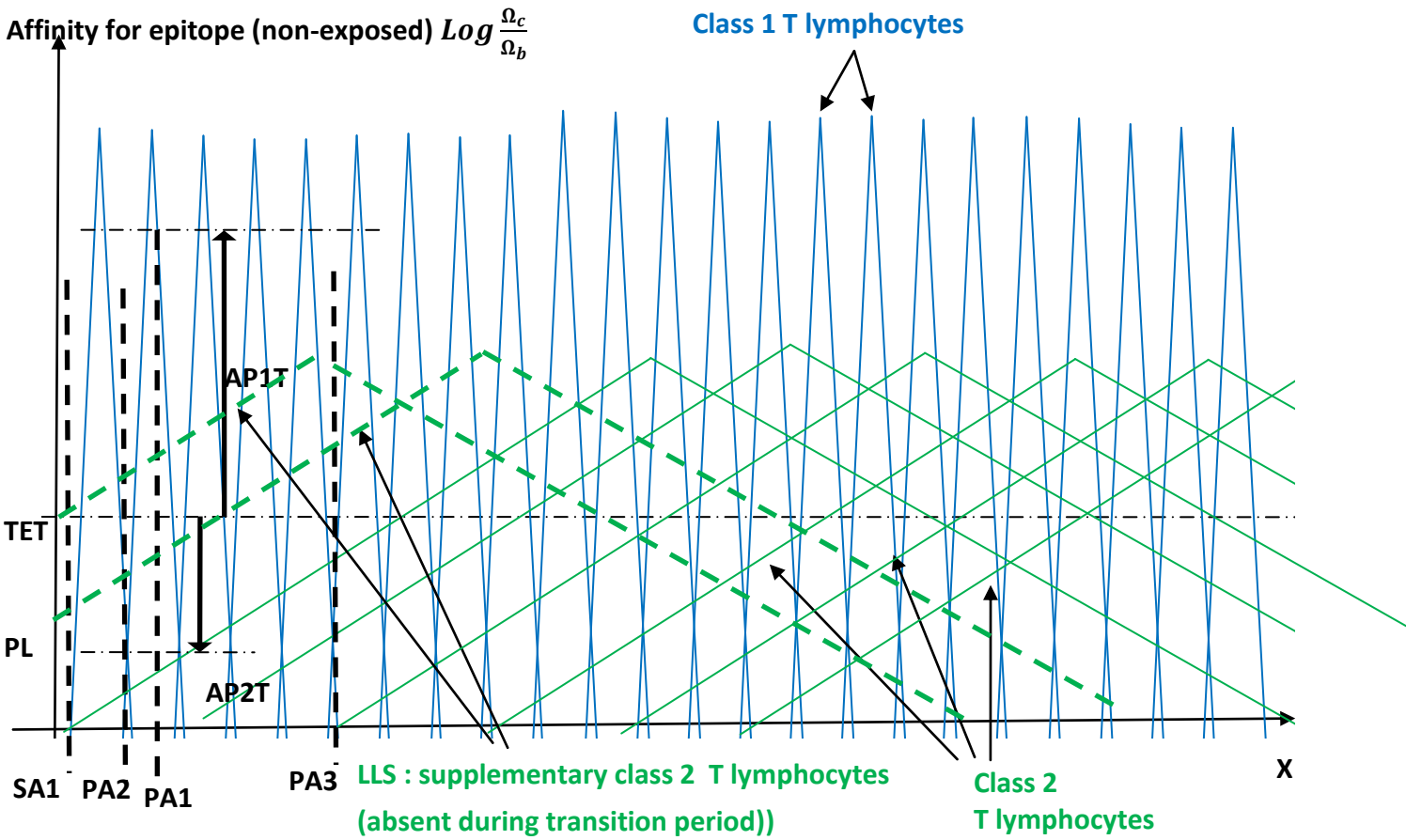

Figure 3: affinity of T lymphocytes for presented epitopes between two self epitopes <u>immediately after a non-exposed to exposed transition</u>. The figure in unmodified as compared to Figure 1 (T lymphocytes are the same as prior to the transition) except that the threshold level for recognition of epitopes is now TET. Epitopes are eliminated by T lymphocytes if the (non-exposed) affinity of the T lymphocyte for the epitope is stronger than TET. T lymphocytes in transit through the thymus are eliminated only if their affinity for self epitopes (SA1) is stronger than TET – which allows supplementary class 2 T lymphocytes LLS to survive, but these supplementary class 2 T lymphocytes are not present immediately after the transition. AP2T: affinity for non-self epitope PA2. PA3: non-recognized epitope distant from self epitope SA1.

Similarly, a period of low immune pressure can allow immunodeficiency viruses to survive after a cross-species transition in hosts that would normally eliminate them, essentially as discussed in section 6.2.1. This leaves the virus with enough time, through successive mutations, to adapt to a progressively increasing immune pressure in the new host and yield epitopes which are in protection gaps in the new host in a appropriate favorable areas of the space of epitopes.

Although the permanent exposure situation is a period of low immune pressure, survival of immunodeficiency viruses that have a major difference in epitopes with their original version is even more favored during low to high exposure transitions as explained in section 6.2.1. Thus, such transition periods are particularly favorable to new virus mutations, whether inter-species or cross-species. In addition, major genotype changes are particularly favored by multiple cross-species transmissions (also see section 7.4). This also implies that the real timing of appearance of new virus variants may be relatively independent of the timing as determined by molecular clock analyses. Mutation rate is strongly accelerated by low to high radiofrequency exposure transitions and cross-species transmission events, which can result in very fast mutations in appropriate conditions, separated by periods of relative stability.

In short, the evolutionary history of immunodeficiency viruses may not be the one which has been written until now. Rather than a constant mutation rate, immunodeficiency viruses have a constant mutation rate in stable conditions, which can be relatively high dependent on radiofrequency exposure details, and short phases of highly accelerated mutation rates, corresponding to low to high exposure transitions and/or cross-species transitions. Further, mutation rates before the onset of

artificial electromagnetic waves may have been a lot lower than modern mutation rates. These findings explain the inconsistencies of the mainstream model with regards to molecular clock dating.

6.2.3 Causation by electromagnetic waves explains late appearance of AIDS and inconsistencies in cross species transmissions.

Mutation rates of any HIV/SIV precursor before the onset of artificial electromagnetic waves were probably a lot lower than after the onset of artificial electromagnetic waves, possibly insufficient to allow virus mutations to outpace host adaptations or to allow immunodeficiency viruses to cross species barriers. This explains the late appearance of AIDS, although it is still somewhat unclear whether relatively benign versions of HIV/SIV may have existed before the onset of electromagnetic waves.

A causal relation between artificial electromagnetic waves and HIV/SIV/AIDS also makes it conceivable that cross-species transmissions were not solely from animal to human: since exposure to artificial electromagnetic waves is a change which affected all species (even though human populations in large cities were particularly exposed), humans are no more the sole species which went through an environmental change expected to have caused the disease to successfully spread.

6.3 The proposed hypothesis is consistent with the timing of the AIDS epidemic.

6.3.1 Starting point of virus divergence.

Assuming that there is a large gap between mutation rates in different exposure conditions, low to high exposure transitions can be viewed as near instantaneous mutations of a virus (or lack of mutation if the virus ends up un-modified), preceded by a stable period in which the mutation rate is negligible and the virus variants are in small numbers, and followed by a period of constant non-negligible mutation rate during which the number of virus variants increases. Therefore, in terms of molecular clock evaluation, the low to high transition is viewed as a starting point at which one new variant is created or picked up and from which the new variant starts to diverge. This analysis justifies that molecular clock analyses of recent and little divergent virus variants which have developed from a single ancestor in the same species and ideally the same sub-species may be used, within certain limits, to determine the date of appearance of the common ancestor. However, molecular clock dating is independent of the origin of the virus which is a starting point for a divergent evolution. For example the origin of such virus may be:

(i) an original stable virus affecting the same host species,

(ii) the occasional expression of an extinct virus conserved in endogenous form, or

(iii) a virus resulting from a cross-species transition from a related host species, or

(iv) a new virus resulting from accelerated mutation of a distinct virus such as HTLV.

It is therefore uneasy to decide if the time to most recent common ancestor (tMRA) of a viral family affecting humans (such as HIV-1 group M) corresponds to diversification of a virus of type (i), (ii), (iii), or (iv), in any case after a low to high exposure transition. In the present approach, low to high exposure transitions are likely to be starting points for the diversification of new intra-species viral families, whatever the origin of the common ancestor.

6.3.2 New pathogenic variants and link with television.

In a high exposure situation there is an increased number of “protection gaps”, thus allowing the virus to diversify. Virus variants possibly existed in non-exposed conditions, but they had co-evolved with the host for thousands of years, so that they were no more pathogenic. The host and pathogen do not have a common history in exposed conditions, so that the new variants that develop in exposed conditions can be pathogenic, unlike the old variants. Since pathogenic variants may in some cases be also more easily transmissible, they are even favored. The diversification process in exposed conditions does therefore almost unavoidably yields to at least some pathogenic variants, which may become dominant if they are also more easily transmissible.

Exposure to electromagnetic waves in Africa started earlier than the onset of Television and may have caused the emergence of HIV. However, until the appearance of Television it was not pathogenic. AIDS seems to have been particularly favored by the onset of Television. This link between AIDS and television broadcasting is confirmed by the following points:

i)The worldwide first confirmed case of AIDS was Arvid Noe, a Norwegian sailor who between august 1961 and may 1962 called at ports on the West African coast (Hooper 1997), including Nigeria which had Television since 1959. He became infected with Hiv-1 group O and later died with AIDS. Arvid Noe was infected with one recent variant, probably in Nigeria which was the only country where he stopped and which had Television. After returning to Europe, the generalized presence of TV broadcasting and electromagnetic waves generally favored the disease, yielding to his death.

ii)Grethe Rask (a Danish surgeon) is probably the first confirmed case who became ill in Africa (i.e. had AIDS symptoms). She set up an hospital in Abumombazi in 1972, then transferred to Kinshasa in 1975 where she became ill with AIDS. Kinshasa had TV

since 1966 and additionally benefited from TV broadcast from neighbouring Brazzaville since 1963. Abumombazi, a lost village well inside congo, probably did not.

iii)AIDS emergence in Haiti in 1979 as evidenced by an outbreak of Kaposi's syndrome (Liautaud et al 1983) coincided with a substantial increase of TV and FM radio emission power in 1977 to 1979 (including the creation of government-controlled radio and TV).

iv) molecular clock dating of HIV 1 group N yields 1963 as the likeliest starting-point (Wertheim and Worobey 2009), corresponding to the onset of Television in a number of African countries including the Kinshasa area, and shortly after the first onset of Television in Africa, i.e. Nigeria in 1959. The emergence of a new viral variant is an indication that there was a significant weakening of the immune response.

Exposure to Television is a major change as it introduced a large bandwidth signal in a range of frequencies which penetrates the human body well, and bandwidth is one of the essential aspects which favors the inhibitory effect INH on which the pro-pathogen effect is based (Lauer 2014b). It is thus not surprising that exposure to Television caused a major change in the evolution of HIV.

7 A consistent picture of the emergence of AIDS.

The consensus opinion is that the ancestor of HIV is an immunodeficiency virus in an animal species, corresponding to the hypothesis (iii) mentioned in section 6.3.1. The present analysis opens up several alternatives: the ancestor of HIV could for be an endogenously conserved virus, a human HIV-like virus, or a different virus. However, detailed examination of available knowledge yields one preferred scenario for the emergence of HIV/SIV, which is discussed in this section: HIV/SIV would descend from HTLV-1/STLV-1. Whilst this preferred scenario is the basis of the present discussion, alternative scenarios exist and are discussed in section 8.

7.1 Comparison of HTLV-1 and HIV.

HTLV-1 has evolved a survival strategy which is adapted to the “old world”, i.e. without electromagnetic waves and thus without “protection gaps”. Its target cells are, like HIV, CD4+ T lymphocytes. Infected CD4+ T lymphocytes over-produce interferon-gamma (Araya et al 2011), which inhibits B cell proliferation (Abed et al 1994), and thus to a certain extent they down-regulate the humoral immune response – as HIV does. HTLV strategy to mitigate the action of destruction by effector CD8+ T lymphocytes (CTLs) is two-fold: on the one hand, it over-expresses certain epitopes against which the immune response is generally low (HBZ epitopes) (Cook et al 2013), which saturates MHC class I antigen-presenting complexes at the cell surface. On the other hand, it stimulates accelerated growth of the infected lymphocytes, which compensate their destruction by CTLs. These mechanisms were developed in the “old world” and do not take advantage of the existence of protection gaps, since there were none.

The survival mechanism of HTLV-1 is rather complex, and most mutations yield non-functional viruses. The number of mutations that yield a mutant able to survive is less than in AIDS so that the in vivo mutation rate of HTLV is 7.10^{-6} per nucleotide base per cycle of replication (Mansky 2000), whilst it is 3.10^{-5} for HIV (Mansky and Temin 1995). The difference is moderate and is unlikely to reflect a better transcription reliability, so we can assume that HTLV and HIV replications per se (excluding the effect of immune pressure) have a similar number of transcription errors. Further, the error rate of the reverse transcriptase alone yields a 20x stronger mutation rate for HIV, which shows that both for HIV and HTLV-1 the in vivo mutation rate is limited by immune pressure rather than reverse transcriptase alone. Viral doubling time in vivo is estimated to 0.65 days (Ribeiro et al 2010). Assuming a virus reproduces each 0.65 days and the reverse transcriptase error rate is $6.\ 10^{-4}$ it takes about 3 years to modify half of the HIV nucleotides by successive mutations, and the conclusions would probably be similar for HTLV-1. Taking into account recombination events diminishes the necessary time, and taking into account immune pressure increases it, yet the figure is compatible with the possibility that HIV may have evolved from HTLV in the first half of the 20th century.

The high mutation rate in favorable conditions is further confirmed by the conversion of HIV-1 to a SIV version which is systematically pathogenic in chimpanzee, which took place in a single chimpanzee host (Mwaengo and Novembre 1998, Novembre et al 2001).

7.2 A scenario for the HTLV-1 to HIV evolution.

Let us assume that one HTLV-1 mutant (I shall call it HTLV-1-L where L stands for loss of functionality) becomes unable to stimulate the growth of infected CD4+ T lymphocytes and instead induces apoptosis of the same. This is probably a common mutation as it is much easier to loose a functionality than to gain one, and as disturbed cells naturally evolve towards apoptosis, which is a safeguard against cancer, unless the disturbance is very carefully adjusted to cause some other outcome.

- when present in a CD4+ T lymphocyte in much smaller numbers than HTLV-1, HTLV-1-L does not prevent co-infecting HTLV-1 to induce accelerated growth of infected lymphocytes, and it can be transmitted to these dividing lymphocytes, so that it can replicate. Its epitopes are not easily detected by the immune system because it is in small numbers so few epitope

presentations by the MHC class I occur, and further because it benefits from the saturation of MHC class I receptors by BHZ epitopes and the like, so that its presence does not yield a significant reaction of the immune system. Thus HTLV-1-L can replicate as a companion virus in HTLV-1 infected CD4+ T lymphocytes.

- In T cell dependent activation of B cells yielding a humoral response against HTLV-1-L, a CD4+ T helper lymphocyte having a MHC class II –restricted HTLV-1-L, non-HTLV-1 epitope as its cognate epitope (ThL lymphocyte) meets an antigen-presenting cell, for example a dendritic cell, which presents its cognate epitope. It recognizes that epitope as its cognate epitope and if it later meets a B cell presenting the same epitope it will activate the B cell. The dendritic cell is likely to be infected by the viruses which epitopes it presents.

If the dendritic cell is dominantly infected by HTLV-1, the ThL lymphocyte detects the HTLV-1 epitopes first, which it will recognize as non-cognate, non-self, yielding temporary inactivation of the ThL lymphocyte (Lauer 2014b) which will thus not detect the HTLV-1-L epitopes.

If the dendritic cell is dominantly infected by HTLV-1-L, the ThL lymphocyte recognizes its cognate HTLV-1-L, non-HTLV-1 epitope, and at the same time it becomes infected by HTLV-1-L during the interaction. It then activates a B cell which migrates to a follicle together with the ThL lymphocyte and proliferates together with the ThL lymphocyte to form a germinal center (Janeway et al 2001). However the ThL lymphocytes being dominantly infected by HTLV-1-L, the antibodies produced by the B cells bind the ThL lymphocytes which are then destructed by the immune system. HTLV1-L does not stimulate replication of CD4+ T lymphocytes, so that (unlike the case of HTLV-1) destructions are not compensated by accelerated replications and the pool of ThL cells is efficiently destructed. Since stimulation by ThL is essential to B cell proliferation, B cell proliferation soon ceases, so that the antibody production directed against HTLV-1-L soon ceases. Thus, whenever a humoral immune response directed against HTLV-1-L starts, it terminates soon. It can thus be said that HTLV-1-L efficiently suppresses the humoral immune response against its MHC class II-restricted epitopes which are distinct from the MHC class II-restricted epitopes of HTLV-1. The HTLV-1-L-specific humoral immune response is suppressed.

Since HTLV-1-L can replicate and since at the same time the humoral immune response against HTLV-1-L is suppressed, the essential barrier to HTLV-1-L propagation is the cellular immune response. Therefore mutations that result in a diminished cellular immune response against HTLV-1 are favored. More specifically, mutations that result in MHC class I- restricted epitopes which are weakly recognized or preferably not recognized by CD8+ effector T lymphocytes (CTLs) are favored whatever their impact on MHC class II-restricted epitopes. Therefore, HTLV-1-L tends to evolve via successive mutations towards a form which is weakly recognized or unrecognized by CTLs after restriction by MHC class I.

However, in the “old world” (i.e. without electromagnetic waves or protection gaps) the HTLV-1-L mutant had no chance for long-term survival independent of HTLV-1. HTLV-1’s survival capacity largely depends on the stimulation of the growth of infected lymphocytes. HTLV-1-L mutations cannot yield complete evasion from the cellular immune system because there are no protection gaps. Since HTLV-1-L has lost its capacity to stimulate lymphocyte growth, it cannot outpace the destruction capabilities of the cellular immune system (CTLs) so that HTLV-1-L mutants unaccompanied by HTLV-1 are killed by CTLs faster than they infect new cells, and they become eliminated.

But, in the “new world” (i.e. with electromagnetic waves and protection gaps), HTLV-1-L, through successive mutation, may reach a form in which it presents only epitopes which are in “protection gaps”, i.e. epitopes which are not recognized by CTLs. This new form of HTLV-1-L escapes both the cellular immune system and the adaptive humoral immune system, so that in essence it escapes the adaptive immune system entirely. Being a self-mimicking pathogen, it is little affected by the innate immune system, so that the immune system is essentially inefficient against it. This new form of HTLV-1-L is thus a HIV-like. Insofar as it conserves even a moderate capacity to replicate, it can infect the host essentially unaffected by the immune system.

Mutations of HTLV-1-L that destruct any basic functionality yield non-functional, non-surviving mutants. Therefore, each surviving mutation must individually preserve the functionality of the original HTLV-1-L proteins, yet change the amino acid sequence of HTLV-1-L proteins so as to minimize recognition by CTLs (and thus change the genetic sequence of HTLV-1-L). This predictable evolution is driven by the need to preserve functionality and by the immune pressure from CTLs, and predictably yields an HIV-like virus which preserves most of the functional organization of HTLV-1 but has a different genetic sequence, adapted to evade the cellular immune system (CTLs).

7.3 Confirmations of the HTLV to HIV evolution hypothesis.

This hypothesis is confirmed by the following facts:

1. the functionalities of the HTLV-1 proteins are essentially conserved in HIV. Possibly the best example is the Rex protein of HTLV-1 and the Rev protein of HIV, which are functionally interchangeable despite different amino acid sequences (Nakano and Watanabe 2012). Functionally, HIV is HTLV-1-L, that is HTLV after the loss of one functionality. Except for the loss of functionality HTLV-1 and HIV differ essentially in their sequence, which HIV has adapted to escape CTL recognition, unlike HTLV which had another survival strategy.

2. HIV-1 / HTLV-1 co-infections are abnormally frequent (Beilke 2012), which shows that the two viruses survive better together than separately and is thus an indication that they have co-evolved for some time.

3. HIV-1 infection progresses faster to AIDS in the presence of HTLV-1 but not of HTLV-2 (Beilke 2012). Both HTLV-1 and HTLV-2 can induce opportunistic infections (Murphy 2004) although the frequency of such infections may be higher in HTLV-1-induced adult T cell leukemia (ATL) (Yaasunaga 2001), but ATL is not involved in HTLV-1/HIV co-infections that evolve to AIDS. The lack of AIDS promotion by HTLV-2 is an indication that AIDS is not favored merely by the diminished immunity which occurs in both HTLVs. Whatever the technical explanations as to the bio-molecular mechanisms which result in HIV-1 being favored by HTLV-1, the fact that it is favored by HTLV-1 is a strong indication that HTLV-1 and HIV-1 co-evolved for some time. Notably, the association of HTLV-1 and HIV-1 favors AIDS but is not reported to favor ATL or any HTLV-1-induced disease, so that it is more likely HIV which evolved in the presence of a stable version of HTLV-1 than the opposite.

4. Many groups of mammals (such as Canidae or New World Primates) do not harbor known leukemia-inducing retroviruses, but all groups of mammals that have known immunodeficiency retroviruses also have retroviruses that induce leukemia (Table 1). If Immunodeficiency Retroviruses had developed independently of Leukemia-Inducing Retroviruses there would not be such a correspondence. Most groups of species that harbor leukemia-inducing retroviruses appear to also harbor Immunodeficiency Retroviruses .

Group of species	**Leukemia-inducing retrovirus**	**Immunodeficiency Retrovirus**
Old World Primates	Simian T-lymphotrophic virus (STLV-1)	Simian Immunodeficiency Virus (SIV) (Keele et al 2009)
	Human T-Lymphotropic Leukemia Virus (HTLV-1)	Human Immunodeficiency Virus (HIV)
Felidae	Feline Leukemia virus	Feline Immunodeficiency Virus (FIV) (Bendinelli et al 1995)
Bovinae	Bovine Leukemia Virus	Bovine Immunodeficiency Virus (BIV) (Zhang et al 1997)
Murinae	Murine Leukemia Virus	LP-BM5 (Cao et al 2012)
Koala	Koala Retrovirus (Denner and Young 2013)	

Table 1: the known leukemia-inducing retroviruses and the known retroviruses that induce AIDS-like disease.

5. The Murine Immunodeficiency Retrovirus LP-BM5 is a mixture of a pathogenic replication-defective virus BM5def and a non-pathogenic virus BM5eco which is necessary for the replication and cell-to-cell spreading of BM5def (Chattopadhyay et al 1989). Both infection of CD4+ T lymphocytes and B cells are necessary for pathogenesis (Li et al 2006). In this case a normal MuLV virus is probably the common ancestor of both BM5eco and BM5def. BM5eco is an essentially normal MuLV virus. BM5def is essentially a MuLV virus which has lost its capacity to induce proliferation of CD4+ T cells and which has probably undergone a series of mutations minimizing its recognizability by CTLs. BM5eco/BM5def is essentially equivalent to HTLV-1/HTLV-1-L couple. If BM5def has lost only its capacity to induce proliferation of CD4+ T lymphocytes, then it may still evolve towards an independent Mouse Immunodeficiency Virus (MIV). But if BM5def somehow has entirely lost its capacity to replicate independently of BM5eco, it may be in an evolutionary dead end. Whether or not it can still evolve to MIV, it is a living animal analog of the intermediate HTLV-1/HTLV-1-L couple which in humans has now “disappeared” insofar as HTLV-1-L has reached its final HTLV-1-independent form, which is HIV.

6. The Central African group of HTLV-1 is nearer to the African STLV-1 than to the Asian or Cosmopolitan HTLV-1 (Liu et al 1996). There is a similar link between the Orang-Utang STLV-1 and the Melanesian group of HTLV-1 (Ibuki et al 1997). An isolated Pygmy strain of HTLV-1 appears more closely related to a corresponding STLV-1 strain than to the dominant Central African HTLV-1 (Yamashita et al 1997). Thus, there is a closer relation between human and simian HTLVs than between different human strains. This is a signature of a (probably ancient) co-evolution of HTLVs and STLVs, which is also reproduced in HIV/SIV. The emergence of HIV/SIV in Central Africa (neither HIV nor SIV were originally present in other continents) (Peeters et al 2008) coincides with the Central African group of HTLV-1/STLV-1, so that as a descendent of HTLV-1/STLV-1 it is logical that HIV/SIV first appeared in a group which was homogeneous for HTLV-1/STLV-1 (African primates including humans) rather than in a group which was not homogeneous for HTLV-1/STLV-1 (humans worldwide).

7. The HIV-1/HTLV-1 synergy extends to other primates as synergy has been evidenced between SIV and STLV-1 in wild African green monkeys (Durand et al 1995), further confirming that co-evolution of HIV-1/HTLV-1 is not limited to the human model.

7.4 A role for cross-species transmissions.

There was probably an independent spontaneous emergence of several immunodeficiency viruses in several species, which is an explanatory factor for the diversity of species which are affected and may develop AIDS-like diseases (Table 1). However, cross-species transmissions are also believed to have an essential role.

7.4.1 Pointers towards cross-species transmissions.

However, the case of human HIV-1 and chimpanzee SIVcpzPtt clearly points towards cross-species transmissions. Genetic proximity of HIV with SIVcpz is a strong indication that at least one cross-species event between human and chimpanzee took place. Further, the close relationship between SIVcpz and HIV goes beyond a mere genetic similarity: the possibility of direct transmission of HIV to chimpanzees was tested in (Mwaengo and Novembre 1998) yielding an AIDS-like disease in the chimpanzee after partial conversion of HIV to an SIV-like virus.

The observations in section 6.1.1. point towards a human to animal or bidirectional transmission. On the other hand, the substantial coincidence between the area affected by VIH-2 and the area where sooty mangabeys live (Peeters et al 2008) is a strong indication that the VIH-2 epidemy depends on the presence of sooty mangabeys, and thus on animal-to-man transmission. There is also a substantial coincidence between the area of origin of HIV-1 in Central Africa and the habitat of chimpanzees and gorillas. Globally, there is evidence of bidirectional transmissions of HIV/SIV between human and animal.

There is a similar link between HTLV-1 and STLV-1 pursuant to point 6 of section 7.3., probably of ancient origin. If the link between HTLV-1 and STLV-1 was only animal to man transmissions, HTLV-1 would have become homogeneous amongst humans after initial transmission from non-human primates. But if there are both human to animal and animal to human transmissions, virus variants that can survive in both hosts are priviledged and local virus variants in human and animal hosts may remain phylogenetically close. The continued closer relationship between local and simian versions of HTLV-1 as compared to different versions of human HTLV-1 is thus an indication of bidirectional transmissions of HTLV-1/STLV-1 between humans of animals.

HTLV-1/STLV-1 and HIV/SIV have essentially the same transmission paths, so that the above observations confirm that these transmission routes are not incompatible with animal to human and human to animal transmission.

The probability of each mutation of HIV/SIV is proportional to the number of cells in each individual in the host species, and to the number living individuals in the host species. The human being has by far the largest [number of cells x number of individuals] amongst all primates and even outnumbers by very far the total number of non-human primates. Therefore, if HIV/SIV appeared first in one species, it is likely that this species was humans. This reasoning is confirmed by the fact that HIV, which initially was non-pathogenic in humans, became pathogenic in humans before it became pathogenic in a few non-human primates, confirming that disease evolution was more advanced in humans than in non-human primates. This reasoning can also be confirmed by a comparison with felids: like humans with respect to simians, the domestic cat outnumbers by very far its wildcat cousins, so that FIV was expected to develop first in domestic cats. Indeed, FIV is already pathogenic in domestic cats but not in wildcats (Pecon-Slattery et al 2008). But there is also a counter-argument: in the early 20th century, non-human primates were in much larger numbers than today in Central Africa (perhaps 2 million chimpanzees) and humans were in much lower numbers (probably around 15 millions in Central Africa). As a wgap, non-human primates may locally have outnumbered humans. Thus the role of the human species in the early 20th century in the initial emergence of HIV may have been less essential than in later steps of the evolution of SIV/HIV.

The above points towards the following: the human species did not solely “receive” HIV/SIV from other primates. It participated in the emergence of HIV/SIV and probably had a pivotal role. Both animal to human and human to animal transmissions have accelerated the emergence of HIV/SIV.

Central Africa is the place in the world where the proximity between humans and non-human primates is highest, because it has more non-human primates than any other place. Non-human primates are commonly used as food and pets (Peeters et al 2002), which multiplies transmission opportunities. Occasional scavenging behaviors of chimpanzees (Watts 2008) may provide a further transmission path. Further, Central Africa is the only place in the world which hosts great apes (i.e. chimpanzees and gorillas) which are genetically nearest to humans. Central Africa is also where the genetic diversity of both humans (Campbell and Tishkoff 2008) and non-human primates is highest. The fact that HIV emerged in Central Africa rather than anywhere else points towards a possible role of cross-species transmission and genetic diversity in the emergence of the disease.

7.4.2 Evolutionary role of cross-species transmissions (independent of recombinations).

The discrete space of epitopes, in which an affinity of lymphocytes for individual epitopes is defined, was already discussed in section 2.2. A discrete space of the virus genetic material can be similarly defined, in which each viral genetic code is associated to an inverse viability of the virus in the host (inversely proportional to viability, wherein viability depends on the host’s immune reaction and on the basic virus functionality). Like was done in section 2.2 for the discrete space of epitopes, an analogy can be made with a continuous space, which will be taken as two-dimensional – and which is not an accurate representation of reality but is useful for explanations.

An elementary mutation in the discrete space of the virus genetic material means a mutation in which a single nucleic acid is modified. Elementary mutations are more frequent than others, although mutations that imply a few nucleotides are also common. An elementary mutation is can be favorable (if it increases viability), unfavorable, or neutral. Viability is determined by the capacity of MHC class I-restricted epitopes to evade recognition by the cellular immune system, by the functionality of viral proteins, and possibly additional parameters. The virus tends to evolve through successive favorable or neutral elementary mutations until it reaches a point in the discrete space of the virus genetic material from which all elementary mutations are un-

favorable. This point is not necessarily the most viable virus sequence: there may be a more viable virus sequence, which cannot be reached by neutral or favorable elementary mutations: the path towards the more viable virus sequence can include several un-favorable mutations, followed a series of favorable mutations. As an example, a mutation requiring two nucleotide substitutions may be favorable whilst each of the individual nucleotide substitutions is unfavorable; in such case the favorable two-nucleotide substitution is unlikely to take place, or at least a lot less likely than if the two nucleotide substitutions were individually favorable. Generally, if the number of required un-favorable mutations is too high, the more viable virus sequence is unlikely to be reached.

In a two-dimensional "continuous space" analogy, each virus sequence is a point in a two-dimensional space (x,y) and an inverse viability function (or surface) z(x,y) corresponding to the inverse of the above-defined viability is defined. Virus mutations tend to go downward the inverse viability surface, and the virus genetic sequence tends to stabilize in "valleys". Where the valley is too deep, the virus sequence is unlikely to get out of it. Thus the inverse of the viability of the virus will be called the inverse viability function, and areas in the discrete space of the virus genetic material in which the inverse viability function has a local minima and in which the viral sequence tends to stabilize will be called "valleys" of the inverse viability function by analogy with a continuous picture.

Different hosts thus have a different inverse viability functions in the discrete space of the virus genetic material, relative to the same virus. Assume that in a single genetically homogeneous "cloned" host sub-species, say host-1, the evolution of HTLV-1 towards HIV yields a HIV-like (say HIV-like-1) which is not necessarily highly pathogenic nor highly contagious. This HIV-like-1 is in a favorable region 1 ("valley" of the inverse viability function) in the discrete space of the virus genetic material. There may be other, more favorable regions, but passing from favorable region 1 to favorable region 2 requires a number of unfavorable mutations to occur before a series of favorable mutations yields to region 2, so that this change is unlikely to occur. Similarly, there may be no direct route from HTLV-1 to the highly pathogenic and contagious HIV-1: all routes may require a number of unfavorable mutations to occur at some point. Indeed, this is a very likely configuration: there is no reason to believe that the configuration of "hills and valleys" in the discrete space of the virus genetic material is such as to permit each epitope to pass from HTLV-1 to HIV-1 through an uninterrupted series of favorable mutations.

But, if HIV-like-1 is transmitted to a host (host-2) which genetic material is near enough from the original host so that HIV-like-1 can survive for some time, yet far enough from it so that HIV-like-1 is not in a "valley", HIV-like-1 will evolve in host-2 towards a new "valley" of the inverse viability function of host-2, corresponding to a modified virus HIV-like-2. If HIV-like-2 is re-transmitted back to the original host-1, it is no more in its original "valley" in the inverse viability function of host-1, so that it can evolve again in host-1 towards a new "valley" corresponding to a new virus HIV-like-3. HIV-like-3 may be more aggressive than HIV-like-1 (i.e. be in a deeper valley of the inverse viability function), in which case it will soon replace HIV-like-1. Thus the passing of the virus through host-2 allowed evolution towards a more viable HIV-like-3, which would not have been possible otherwise, or at least would have taken a lot of time. A practical example of this, assuming HIV-1 was originally transmitted to humans by chimpanzees in which the original virus was non-pathogenic, is the fact that HIV-1, when transmitted back to a chimpanzee, mutated very quickly (i.e. on a single host) towards a new SIV version which is systematically pathogenic on chimpanzee (Mwaengo and Novembre 1998, Novembre et al 2001), making it apparent that passing through humans had increased its viability and pathogenicity in chimpanzees. We do not know whether HIV-1 comes from chimpanzees or not, but there is a possibility that HIV/SIV may have been transmitted several times from human to chimpanzee and vice versa.

Thus, the passing of HIV-likes through successive genetically different hosts accelerates its evolution towards a more viable variant, which may also be more pathogenic. In particular, in a configuration which includes a numerically dominant species, passing of the virus through other species accelerates its evolution in the dominant species. In a configuration in which there is more intra-species genetic variation, the virus evolves faster than in a genetically homogeneous species. Therefore, the greater genetic diversity of humans in Africa and the passing of the virus through non-human primates accelerated the evolution of the virus in Central Africa, as compared to other areas, which explains why HIV emerged in Africa rather than elsewhere. Yet, it primarily accelerated the evolution of the virus towards a version which is highly viable in the numerically dominant species, i.e. humans, rather than in other species through which the virus was originally passed in forms which were adapted to the dominant species, i.e. humans, and were less viable in non-humans. This could explain why HIV/SIV possibly reached pathogenicity levels in humans first.

A contrario, the lack of immunodeficiency virus in koalas to date would be due to the fact that koalas have few interactions between individuals and are an isolated species, leaving few possibilities for cross-species transmission events.

7.4.3 Cross-species recombination events.

The above-discussed acceleration of SIV/HIV evolution due to cross-species transmissions is independent of possible recombination events. However cross-species transmissions also allow very different SIVs to occasionally co-exist in the same host. Such co-existence induces recombinations, which also accelerate the evolutionary process. For example, the SIVcpzPtt affecting central (P.t.troglodytes) chimpanzees would be a recombination of SIVrcm and SIVgsn (Bailes et al 2003). But since this SIVcpzPtt is phylogenetically very near to HIV-1-M, the recombination may have taken place in a human host or in a chimpanzee host. Recombination is unlikely to have taken place in another host because the recombined SIV is adapted to humans and chimpanzees, but it would have been recognized by the cellular immune system and eliminated in any other host.

7.4.4 Limited viability of immunodeficiency viruses after a cross-species transmission.

Whilst cross-species transmissions of specific SIV versions can yield AIDS-like disease in affected species, it appears that in most cases of natural animal to human transmission an antibody response exists, which can be detected by ELISA tests, yet the SIV virus remains un-detectable by PCR amplification of DNA (Djoko et al 2012). Here the invading SIV is in a "valley" of the inverse viability function in the original simian host but not in the human host, so that the cellular immune response is efficient against it, and this invading SIV is prevented from replicating in T lymphocytes, so that it is not detectable by PCR amplification of DNA extracted from the blood. Nevertheless, it still generates a humoral immune response during the initial phase of infection before the onset of the cellular immune response. This initial humoral immune response is possibly suppressed due to elimination of CD4+ helper T cells neutralized by the antibodies (see section 4); but it may also re-appear in later stages after a mutation of the SIV strain infecting these CD4+ helper T cells, in which case it is inefficient against the dominant SIV variant .

In such infections SIV may still exist in the plasma in the form of free virions (which are not detectable by DNA amplification) and may still be replicating in immunologically privileged areas such as the eyes or testes. If the SIV-infected human is also infected by HIV or by another SIV, recombination events do occur and if yielding a variant which is capable of evading the human host's cellular immunity, such recombinants may become the dominant variant and even evade the human host's immune system, causing a novel HIV lineage to emerge. Whether or not there is a co-infection with another SIV, the invading SIV can evolve through mutations and if yielding a variant that escapes the immune system it may re-emerge and invade T lymphocytes.

Possible existence of free virions also implies that the virus has a limited but existing capability to survive in the host, and possibly to be transmitted by the host, despite being recognized by the host's cellular immune system. If the host is or becomes infected by HTLV-1, the SIV virions may enter HTLV-1 infected CD4+ T lymphocytes and replicate in these lymphocytes, taking advantage of the protective effect of HTLV-1 (see section 7.2). This results in increased viremia, increased recombination opportunities if several distinct SIVs are present, possible onset of immune deficiency, and the possibility for SIV to be transmitted as a companion virus of HTLV-1. Indeed, the presence of HTLV-1/STLV-1 may still be largely necessary for the replication, mutation and recombination after natural cross-species transmission of HIV/SIV versions which are not adapted to the receiving species. This could also explain why immune deficiency viruses which today can survive independent of their associated leukemia-inducing virus in their natural host do not appear to have been transmitted to hosts that are not naturally infected by leukemia-inducing viruses.

7.5 Miscellaneous questions.

7.5.1 Are macaques particularly susceptible to SIV ?

Cynomolgus monkeys (crab-eating macaques) experimentally inoculated with SIVagm (from African Green Monkeys) became infected but did not develop AIDS-like disease (Honjo et al 1990). Infection of Rhesus macaques inoculated with SIVagm did not cause AIDS-like disease. Infection of four rhesus and four pig-tailed macaques yielded a significant decline in circulating CD4+ lymphocytes in only 2 out of 8 macaques (Johnson et al 1990). Thus in most cases macaques do not develop AIDS-like disease after experimental infection with an SIV from another species.

Pig-tailed macaques infected by SIV from an African Green Monkey developed a disease which resembled AIDS (Hirsch et al 1995). However, although the disease was an immune-deficiency disease, it had notable differences as compared to AIDS. A number of infected animals developed overwhelming bacterial infections, which is unusual in AIDS. In a typical acute case of disease development, both the numbers of B cells and CD4+ T cells dropped. Based on these differences, the observed disease was not AIDS.

The inoculated SIVagm was not adapted to pig-tailed macaques and was therefore recognized by the cellular immune system. However, the number of inoculated virions was large as compared to a natural infection. The inoculated virions infected lymph nodes and B cells before the onset of the primary cellular immune response. After onset of the cellular immune response, CTLs attacked B cells that had been infected, causing B cell depletion, suppression of humoral immune response and sensitivity to bacterial infections. Disease course was faster than usual. In short, unlike AIDS, the disease course did not reveal a lack of recognition by the cellular immune system but rather an excellent recognition, as expected for infection with a non-adapted SIV.

Many experiments on macaques were made with "SIVmac" viruses which had been passed through macaques and may have become adapted to macaques, possibly yielding AIDS-like disease in a manner comparable to HIV.

Thus, there is no evidence that macaques are overly sensitive to SIV viruses infecting other species. Rather, the evidence is that macaques, as expected, are sensitive to SIVs adapted to macaques (if any).

7.5.2 Are African primates protected from SIV ?

After a cross-species transmission, SIV optimizes its genetic formula to survive in the new host species, i.e. it reaches a "valley" in the inverse viability function of the host species. A first optimization may occur quickly in a single infected animal as was the case in (Mwaengo and Novembre 1998) but the virus may need some intra-species transmissions before reaching a temporarily stabilized viral genetic sequence. Animals in which the stabilized viral sequence causes short term death die quickly.

If sampling any animals some time after initial SIV invasion, only those which can live with the disease are found, because others have died. This is not a long term adaptation but rather the consequence of a short-term death toll. The surviving animals can withstand SIV because the stabilized SIV does not escape entirely the immune systems of those animals, although it may have escaped entirely the immune systems of the dead animals (if any). This does not protect the surviving animals from SIV generally: after passing through a distinct host species a returning, a modified SIV which will stabilize in a different "valley" as compared to the original SIV may again cause deaths in the previously surviving animals. An example of this is the epidemic of AIDS-like disease in chimpanzees (Rudicell et al 2010).

A further cause of apparent non-sensitivity to SIV is the fact that SIV is just as recent as HIV. In a number of non-human primates, SIV may not yet have evolved to a severe disease-causing form, merely because the number of animals in each species is insufficient to permit as fast an evolution as on the human being. This is particularly obvious in African Green Monkeys: Caribbean-born African green Monkeys have the same non-pathologic disease course as African-born ones (Pandrea et al 2006) despite the fact that Caribbean-born African green monkeys are not infected by SIV in their natural environment, thus confirming that the non-pathologic character of the infection in African green monkeys is not due to a selection of surviving animals.

African primates sampled in the wild are thus generally little susceptible to the SIV strain which infects them (if any) but may occasionally be susceptible to other SIV strains, as happened to a chimpanzee which developed an AIDS-like disease after being contaminated with HIV (Mwaengo and Novembre 1998).

8 Age of HIV/SIV and alternative scenarios.

The replication rates of HIV as discussed in section 7.1 and the discussion in section 7.2 support the hypothesis that an initial HIV/SIV precursor appeared after the onset of artificial electromagnetic waves out of an evolution of HTLV-1 (**1st (main) scenario**). However other possible scenarios exist as to the origin of the first HIV precursor, which do not modify the fundamental idea that HIV/SIV evolved towards its modern form and became pathogenic because exposure to electromagnetic waves created "protection gaps" which it could use to evade the immune system.

A major alternative scenario is that a HIV/SIV precursor derived from HTLV-1 may have appeared earlier than the onset of electromagnetic waves and remained a non-pathogenic companion virus of HTLV-1 for thousands of years (**2nd scenario**). According to the discussion in section 7.2 it is essentially the final step of becoming independent of HTLV-1 which is excluded in a non-exposed situation; but an ancient evolution of an HTLV-1-L version towards HIV/SIV precursors in a non-exposed situation, although much less favored than in an exposed situation, cannot be entirely excluded. In this case, the appearance of artificial electromagnetic waves would have allowed an HIV/SIV precursor to finalize its development so as to totally evade the cellular immune response using protection gaps, which it was unable to do before, thus allowing it to survive independently of HTLV-1. Molecular clock datings based on modern mutation rates and concluding to a more recent emergence, once corrected for the much slower mutation rate of HIV/SIV precursors in the absence of electromagnetic waves, would not exclude this second scenario.

An argument in favor of the second scenario is the finding that SIV is present on the island of Bioko which was separated from mainland 10,000 years ago (Worobey et al 2010). However, Bioko hosts the capital city of Equatorial Guinea, with a population of 260,000 inhabitants in 2001. It is thus a busy place with intense human exchanges with the continent. Pet monkeys or bushmeat imported from the continent may have resulted in transmission to local monkeys of continental SIV viruses in a very recent period, so that the presence of SIV on Bioko is not a reliable indication that SIV would have existed before the onset of electromagnetic waves.

The second scenario is further supported by a claim that SIV was found in found in conserved remains of ancient Egypt monkeys (Goudsmit 1997). A similar search in skins conserved in a primate museum is mentioned in (Mindell et al 1995) as "in review". However neither led to a publication in a peer-reviewed journal, which in view of the relatively uncontroversial nature of such claim is a sign that results were not clear-cut. No other similar search in conserved primate skin was found in the literature. In view of the fact that such a search successfully retrieved Koala Retrovirus in 120-year old museum skins (Avila-Arcos et al 2012), and in view of the much higher importance of the origins of HIV/SIV as compared to the origin of Koala Retrovirus, the lack of any peer-reviewed publication of a finding of SIV in conserved museum skins is at least an indication that SIV did not exist before the 20th century.

The lack of SIV in Caribbean green monkeys (Daniel et al 1988), which descend from animals exported from Africa in the 17th century, is also an indication that SIV is recent, although it could be due to chance in view of the limited genetic diversity of these animals (Lekutis and Letvin 1995).

Considering the above arguments, the second scenario is viewed as somewhat less likely than the first, but the issue cannot be considered as sorted out.

Interestingly, whilst HIV/SIV may be a descendent of HTLV-1, HTLV-1 may be a descendent of an ancient immunodeficiency virus. In view of the observed "fossil" endogenous lentiviruses in several species of mammals (Katzourakis et al 2007, Han and

Worobey 2012, Gifford et al 2008…), lentiviruses existed in mammals roughly 10 million years ago, possibly comprising immunodeficiency viruses. If immunodeficiency viruses appeared in "naïve" mammals 10 million years ago, it probably took millions of years for mammalian immune systems to overcome these immunodeficiency viruses and for immunodeficiency viruses to mutate to HTLV-like viruses which are less dangerous but can survive with modern immune systems (without electromagnetic waves). The fact that HIV is functionally simpler than HTLV-1 somehow implies that it may have appeared earlier. The fact that HTLV-1 may be a descendent from an ancient immunodeficiency virus also implies that there exists a "pre-existing" evolutionary path between the two, which may have facilitated the backward mutation from HTLV-1 to HIV.

This finding opens up some further possibilities:

3rd scenario: a HIV/SIV precursor may descend of an ancient immunodeficiency virus through an un-interrupted lineage, the synergy between HIV/SIV and HTLV-1/STLV-1 being due to the HIV/SIV origin of HTLV-11/STLV-1. This third scenario is viewed as less likely than the first (main) scenario for essentially the same reasons as the second scenario.

4th scenario: a HIV/SIV precursor may descend from an ancient immunodeficiency virus conserved in endogenous form and occasionally expressed, which recovered its capacities of exogenous survival after the onset of artificial electromagnetic waves. The fact that an endogenous human retrovirus can be expressed as an exogenous viral-like particle was verified in (Boller et al 1993). This fourth scenario is not privileged because the known human endogenous viruses (HERV) do not appear to be immunodeficiency viruses; but no extensive search of the human genomes was made, in particular because only a few individual human genomes were sequenced until now.

Finally, one cannot exclude the possibility of a "mix" between these alternatives, possibly involving recombinations of viruses having different origins.

9 Conclusion.

Antigen variation and self mimicry are the basic characteristics required for a pathogen to best take advantage of a permanent exposure to electromagnetic waves. Amongst self-mimicking pathogens capable of antigenic variation and affecting humans, bacterias and protozoas are limited by the limited number of variants of their surface proteins. Owing to an inherent capability to suppress the humoral immune system, HIV appears as the sole virus which can escape the immune system entirely by adapting its proteins to avoid recognition by CD8+ T lymphocytes after restriction by the MHC class I. The hypothesis that the emergence of AIDS/HIV was caused by the appearance of artificial electromagnetic waves is thus a logical inference from the basic properties of HIV, which extends to other immunodeficiency viruses. It solves several inconsistencies of the mainstream consensus, including molecular clock inconsistencies, inconsistencies in cross-species transmission events, and the fundamental question of why immunodeficiency viruses and diseases did not emerge earlier. It is consistent with known biological properties of HIV. It is also consistent with the early history of HIV and with its known biological properties. These findings substantiate the hypothesis that there is a causal relation between exposure to permanent electromagnetic waves and AIDS.

Additionally, the hypothesis makes it possible to propose several scenarios for the emergence of HIV/SIV. According to a preferred scenario, which yields a complete and consistent picture of the emergence of HIV/SIV, a predictable evolution of HTLV-1/STLV-1 in the presence of man-made radiofrequency emissions, accelerated by cross-species transmissions to and from non-human primates and by genetic diversity within the human species, would have caused the emergence of HIV/SIV. Whilst such scenarios are essentially built on accepted knowledge, the appearance of "protection gaps" in mammal's immunity due to the onset of artificial electromagnetic waves would have provided for the possibility of HIV/SIV survival independent of HTLV-1/STLV-1, which explains the sudden appearance of HIV and probably SIV in the 20th century, and the emergence of AIDS after the onset of Television in HIV-affected areas.

The hypothesis presented in the present paper implies that the presence of artificial electromagnetic waves probably remains essential for the development of AIDS and the survival of HIV. This aspect of the hypothesis could be tested by installing recently infected persons in an environment free of artificial electromagnetic waves and observing the evolution of the disease. However, the interaction of electromagnetic waves with the immune system is complex and it may be necessary to take some precautions to avoid interference with other effects. For example, brutally entering an environment which is free of artificial electromagnetic waves causes a transient pro-auto-immune effect as per Table 1 column E of (Lauer 2014b), which may be detrimental. Also, a loss of immunity cannot be excluded as a number of effector T lymphocytes may be unable to survive both positive selection in the presence of electromagnetic waves and suppression by regulatory T lymphocytes after complete cessation of exposure, particularly in persons who were previously exposed to relatively high power artificial waves. Verification of the present hypothesis also presents some material difficulties as an open environment free of artificial electromagnetic waves does not exist and it may be necessary to use high-performance Faraday cages. Also, the action of electromagnetic waves through the immune system as described in (Lauer 2014a,b) may not be the sole interaction of AIDS with electromagnetic fields, so that unexpected effects cannot entirely be ruled out. For example, it would also be advisable to take care of possible interference with the findings in (Montagnier 2009, 2010) which, although unexplained, have not been proven to be due to experimental errors and thus could potentially affect experimental results. However, within a carefully designed protocol and possibly after some preliminary tests, it should be possible to experimentally verify the present hypothesis.

If the present hypothesis is verified, it will open up a possible path towards eradication of AIDS, through suppression of artificial electromagnetic waves, and it will provide a short-term alternative to tritherapies, through use of Faraday cages or stays in “white zone” areas where exposure to electromagnetic waves is low enough.

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