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Total-Body Positron Emission Tomography (PET) Imaging in Infectious Diseases

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Role of PET Imaging in Infectious Diseases Clinical Care and Pathogenesis Research

PET imaging has an important role in infectious disease pathogenesis-based research and clinical care[1,2]. [^{18}F]fluorodeoxyglucose (FDG) is preferentially taken up by inflammatory cells and macrophages in the tissue[3,4], and has been the mainstay of molecular imaging in viral, bacterial and fungal infections[5,6]. However, the role of FDG PET imaging is somewhat limited in its role in the diagnosis and treatment of various infectious pathogens given the non-specific nature of tracer uptake and limitations of sensitivity, especially in the setting of concomitant malignancies and disorders of immune regulation and inflammation[7]. As a result, novel infectious disease molecular imaging strategies are on the forefront of clinical and pathogenesis-based research. These approaches are broad, and include immunoPET incorporating antibodies or antibody fragments/minibodies targeting pathogen-specific antigens or cells responsible for immune responses and drugs that target various pathogen-specific metabolic or enzymatic pathways[1,2,8]. The recent Covid -19 pandemic has prioritized investigation of communicable diseases and so it is timely that PET research should contribute to the global response. Molecular imaging in infectious diseases and associated morbidities involve the following general foci:

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1. Pathogenesis based research to determine the location and extent of infection, associated innate and adaptive immune responses, and inflammation (both detrimental and beneficial). Imaging of associated comorbidities, including multiple organ inflammation (*e.g.* vascular, central nervous system, pulmonary inflammation), is also a critical component of this pathogenesis-based research that has direct clinical relevance, especially the setting of acute or chronic viral diseases such as COVID-19 and HIV[1,2,7,9].

2. Diagnostic studies to determine specific pathogens or groups of pathogens (*e.g.* HIV, enterobacteriaceae, mycobacterium tuberculosis) using novel immunoPET tracers that directly engage pathogen antigens/proteins directly or other drugs that target unique metabolic or enzymatic pathways[2,7,10–13].

3. Determining responses to antimicrobial and antiviral therapies. These responses may include direct pathogen burden and location, longitudinal assessment of immunologic, inflammatory responses, and associated comorbidities[1].

4. Imaging of host cellular receptors and other targets of infectious pathogens. These are diverse and may include, for example, imaging density and distribution of ACE-2 receptors used by SARS-CoV-2 for cell entry and replication, CD4 and other viral coreceptors used by HIV to engage host cells[10,14].

5. Total-body tissue distribution and pharmacokinetic/pharmacodynamics of various antimicrobial drugs and other anti-infective small molecule or biological agents.

6. Metabolic disturbances or other clinical factors that may lead to increased susceptibility or morbidity from various infection pathogens.

A classic example of how decades of molecular imaging experience has been applied to studying various aspects of chronic (and acute) viral infections is PET imaging in people with HIV and animal models of HIV or simian immunodeficiency virus (SIV) infection. In addition to its profound disruption of the cellular immune system and loss of CD4 T cells over time in untreated infection, HIV infection has been associated with increased cardiovascular disease, metabolic dysregulation, neurological disorders, and various hematological and solid-tumor malignancies[15,16], even in the setting of otherwise suppressive antiretroviral therapy. As a result, PET imaging has been used to: (1) localize and characterize tissue measures of inflammation and cardiac disease using FDG, (2) characterize neurological outcomes of viral infection including neuroimaging of various metabolic pathways, dopamine transport, and cellular activation, (3) determine anti-retroviral (ART)-related toxicities, (4) quantify changes in various immune cell types, such as CD4+ T cell distribution, and, (5) directly visualize areas of persistent HIV infection in the setting of otherwise suppressive ART, as we have recently reviewed[7].

Clearly, these types of PET studies can and are being applied to other viral and bacterial infections, with a more recent surge of interest in various imaging modalities to characterize SARS-CoV-2 infection and related immune responses and inflammatory morbidity[17,18]. Nonetheless, major limitations using standard PET imaging technologies have been identified as described below, and novel molecular imaging approaches for the clinical

and pathogenesis-based research of various infectious pathogens are urgently needed[1,2]. High sensitivity, total-body PET imaging strategies have major potential to overcome these challenges and revolutionize non-invasive infectious disease research.

Advantages of Total-Body PET Imaging

The most advanced form of molecular imaging of the human body, total-body PET, is being introduced into clinical use[19–22]. Less than 1% of the photons emitted during traditional PET scanning are detected given the limited axial field of view and body length (typically <25cm) that can be imaged at one time. The field of view in total-body PET platforms, such as EXPLORER or PennPET Explorer, is extended over the entire individual (1-2 m) by using a large number of parallel detectors that simultaneously detect photon emission [21,23,24,25l,26]. These platforms accept more coincident positron decays that may be used to maximize sensitivity while introducing only slightly degraded axial spatial resolution and a small increase in scatter fraction. As a result, early data suggests that total-body PET provides a >40-fold gain in effective sensitivity and a >6-fold increase in signal-to-noise ratio compared with standard PET[27]. These dramatically enhanced performance characteristics allow for decreased PET scanning times acquiring data “total-body wide” and may be leveraged to decrease the amount of radiotracer required, thereby permitting more frequent imaging or longer imaging periods during radiotracer decay. This is of particular value for imaging agents labeled with longer-lived radionuclides such as ^{89}Zr, which have disadvantageous dosimetry properties and must therefore be administered in much smaller amounts than, say, ^{18}F-labeled radiotracers. The combination of full field of view and enhanced temporal resolution in total-body PET imaging also allows for improved dynamic quantification of radiotracer uptake over time.

Potential for Total-body PET Imaging in Infectious Diseases

High sensitivity total-body PET has potential to dramatically improve molecular imaging and systems biology approaches in fields such as oncology, bone metabolism, inflammation and cardiovascular medicine[19,28–31], as discussed in the other chapters of this issue. However, applications to infectious disease research and clinical care are just now emerging, but may address several limitations of traditional PET imaging as follows:

1. Direct visualization of low-level specific pathogen or host pathogen-interactions.

The direct visualization, anatomical localization and quantitation of viral and bacterial diseases can be extremely challenging. For example, chronic viral infections that are able to maintain some state of latency under either natural immune control (*e.g.* various human herpes viruses such as cytomegalovirus and Epstein Barr virus) or under the cover of antiviral therapy (*e.g.* HIV) express very low levels of viral proteins (*i.e.* low infectious burden), and can persist in locations that are difficult, if not impossible, to sample directly[7]. For example, HIV may infect a very small number of mononuclear cells in the setting of ART (*e.g.* <1 infected CD4 T cell per million cells in the circulation), and much of the viral genetic material is quiescently integrated into the human genome[15,16]. HIV also largely resides in organized lymphoid or other tissues outside of the peripheral circulation, such as gut-associated lymphoid tissue or lymph nodes, and many anatomical regions are

inaccessible to routine sampling. Chronic bacterial disease, such as latent mycobacterium tuberculosis may also persist in very low burdens in immune privileged anatomical sites, including tissue outside the pulmonary system[1,2,32]. In addition to low pathogen burden or protein production, there is potential for variability in gene sequences between and within individuals and suboptimal engagement of tracer molecule to targets. As a result, there is a need for whole body molecular imaging platforms with high sensitivity and improved signal/noise ratios over standard PET imaging platforms to visualize the limited disease reservoirs.

In addition to the examples above, increased sensitivity from total-body immunoPET [*e.g.* radiolabeled pathogen-specific monoclonal antibodies (mAb)] may also be particularly relevant in acute viral infections that manifest in highly morbid disease, such as COVID-19. Whereas individuals with SARS-CoV-2 infection may shed viral RNA in the respiratory tract weeks after onset of symptoms[33], replication appears to be predominately restricted to respiratory mucosa. However, given the extent of multiple organ dysfunction and inflammatory cascade observed in COVID-19[34], there may be more widespread tissue viral cytophatic effects that are far more subtle than the observed in the respiratory tract. These sites also present challenges to direct investigation through invasive means, necessitating PET imaging strategies that are highly sensitive and able to detect low-level signal from background noise.

Highly sensitive, total-body PET also has the potential to enhance molecular imaging of cellular targets of viral infection required for efficient replication. For example, current immunoPET strategies are being used to image CD4 expression in the setting of HIV/SIV[10,14], and there is intense interest in visualizing ACE-2-expression in the setting of COVID-19. Whereas traditional PET may have sensitivity to visualize expression of such target in organized lymph node or pulmonary tissues, increased sensitivity and signal/noise ratios will likely be needed to identify and quantify expression in other tissues which may play a role in whole body pathogenesis and organ involvement. Such sensitive non-invasive, total-body surveys may also allow predictions of disease severity and clinical outcomes.

2. Biokinetic imaging of immunological response to infection.

Persistent cellular immune responses following viral infection may be subtle and require longitudinal imaging in order to understand pathogen-specific responses and to inform on systems-based immunology approaches. Specific examples of CD4 and CD8 T cell imaging are discussed below, but will likely require high sensitivity total-body imaging and longitudinal imaging requiring multiple doses of tracer with reduced radiation risk to individuals.

3. Inflammatory consequences of infection and other pathogen-related comorbidities.

Inflammatory responses to various infections can be profound and long lasting[34]. For example, SARS-CoV-2 can lead to dramatic increase in soluble markers of inflammation and coagulopathy that persist for weeks to months following cessation of viral shedding and resolution of viral replication[34]. Whether or not low-level, persistent immune activation is associated with individuals that experience chronic COVID-19 symptoms (“long haulers”) is not known, but even in the setting of normalized circulating inflammatory markers, there

may be more subtle and persistent tissue foci of cardiopulmonary, lymph node and other tissue inflammation or fibrosis that would require high-sensitivity imaging. A large body of FDG-PET imaging studies of SARS-CoV-2 has recently emerged reporting pulmonary hypermetabolism consistent with an active inflammatory process along with increased associated lymph node tracer uptake[17]. More recent published data suggest that these findings are not isolated to the lungs, and may involve other organs such as the salivary glands[18], bone marrow, spleen, and nasopharynx[18].

HIV also leads to chronic immune activation and inflammation leading to increased cardiac, immunological and neurological morbidity, even in the setting of long-term antiretroviral use. FDG PET has been implemented in both of these viral infection[15,16] but limited by sensitivity in treated chronic HIV or convalescent COVID-19 and by the radiation dose limitations inherent in longitudinal imaging studies.

4. Tissue distribution and Kinetics of anti-infective agents.

Pharmacokinetic/pharmacodynamic (PK/PD) studies used in traditional early phase clinical development of antimicrobial and antiviral agents rely on frequent peripheral blood sampling to establish drug kinetics and elimination in the circulation. These data are also used to evaluate drug efficacy or biological effects *in vivo*. However, there is a paucity of data regarding drug dynamics in tissues, which are the primary sites of antimicrobial and antiviral activity[35,36]. Drugs may distribute rapidly throughout tissues preventing whole body PK evaluations. Examples of dichotomies between tissue and circulating blood drug levels are very common. For example, cerebrospinal fluid drug levels may be different from levels within the brain parenchymal itself. As a result there has been interest in using PET imaging of radiolabeled drugs to look at the tissue-wide biodistribution and kinetics of various anti-infective agents[37]. The potential for PET imaging to inform on PK/PD was demonstrated by a recent animal and human study of [^{11}C]rifampin in the setting of tuberculous meningitis[38]. This study demonstrated that rifampin penetration into TB-infected brain lesions was limited, heterogeneous in distribution and decayed rapidly over time[38]. PET data was used to established PK models to predict a higher dose of drug to be used to achieve therapeutic parenchymal concentrations[38].

Our group is currently conducting clinical PET studies to determine the early tissue distribution and kinetics of raltegravir in people with HIV on ART. Raltegravir is a strand-transfer HIV integrase inhibitor, a commonly used class of antiretroviral in combination ART. Certain immune privileged environments are important foci of HIV persistence in the setting of ART and many of these loci may have achieve suboptimal ART drug levels, leading to ongoing low level viral production and persistent immune activation[39]. These drugs are rapidly and efficiently absorbed and distribute rapidly throughout tissues. However, very little information is known about tissue-penetration of drug where active HIV infection may persist. Figure 1 shows representative PET imaging of [^{18}F]Raltegravir using traditional imaging methods hours after intravenous drug administration. PET imaging of [^{18}F]Raltegravir provides a unique opportunity to image total-body drug PK. However, current PET methods using serial imaging time points to determine biokinetics of drug requires multiple bed positions and certain areas have revealed very low to no detection of

drug, such as the brain, that may represent radioactive drug concentrations that are below the sensitivity threshold.

As a result, there is an urgent need for total-body PET platforms, that have increased sensitivity and signal/noise ratios. In addition, these total-body scanners also allow imaging derived arterial blood time course of a radiotracer providing an arterial input function to the body's tissue uptake. This information significantly simplifies the process of quantification of the tracer's binding in tissues, and the results may be presented as whole body quantitative, functional parametric images[24]. The improved sensitivity also allows tracers to be followed over longer periods of time as the radionuclides decay.

5. Tracking responses to biological and immunotherapies for viral infections.

Similar to cancer research, there has been intense interest in using cell-based therapies for various chronic viral infectious diseases. These approaches range from exogenous infusions of allo-donor viral-specific T cells to chimeric antigen receptor (CAR) T cells designed to target proteins such as the HIV envelope[40]. Many of these therapies require expansion of pathogen-specific cells upon engagement with target antigen, but it is challenging to determine the longitudinal kinetics of donor cells across tissues and time without invasive sampling[40]. These cells may have limited access to various anatomical compartments such as lymph node follicles, that contain a majority of the HIV reservoir[41], and the central nervous system, another important, but understudied are of viral persistence[42]. PET imaging of CAR-T cell therapies has been implemented in cancer[43], and there is intense interest in having the ability to follow various cellular therapies in the setting of infection that can track cell distribution, turnover and persistence over time. However, non-invasive PET imaging modalities will need high sensitivity and allow for longitudinal imaging with several time points and multiple radiotracer administrations while keeping radiation doses to acceptable levels. Total-body PET is ideal for this undertaking.

Example of Molecular Imaging of Immune Responses to Infectious Diseases Highlighting the Need for Total-Body PET Imaging

ImmunoPET imaging of CD4 T cell dynamics in SIV/HIV infection.

CD4+ T cells are the main target of HIV infection. Active disease leads to subsequent and profound reduction in CD4+ lymphocytes throughout the blood and tissues. While counts may improve in many individuals on ART, lasting perturbations to tissues such as the lymph nodes and gut-associated lymphoid tissues are common[15,16]. As a result, there has been interest in CD4+ T cell specific PET-based imaging techniques to follow CD4+ T cell dynamics and recovery during natural infection and following various immune-based interventions. For example, a recent investigation of the use of an α4β7 mAb in acute SIV infection in macaques demonstrated sustained virological control in mAb treated monkeys[44]. While this major finding has yet to be confirmed in subsequent studies using a different and more replication competent SIV strain, the study involved PET-CT imaging using a ^{64}Cu-labeled F(ab′)2 antibody against CD4 to demonstrate repopulation of CD4 T cells in a number of tissues, including gut[14]. The reconstitution of gut CD4 T cells was unexpected based on the original study hypothesis that the α4β7 mAb would interfere

with CD4+ T cell trafficking to these areas [44]. As a result, this study is proof of concept of how imaging various cell-specific markers may provide critical information regarding whole-body immune responses over time. However, similar studies are challenging in the setting of human HIV infection given the need for longitudinal study design incorporating multiple radiolabeled antibody infusions and the subsequent need to reduce radionuclide dose. Human studies would also benefit from the use of radiolabeled mAbs with longer half –lives (*e.g.* incorporating ^{89}Zr]. Whereas ^{89}Zr has a 78h $t_{1/2}$ and can be imaged up to a week or so following administration using traditional PET, high sensitivity total-body imaging may allow serial imaging over 2-3 weeks following a single administration of tracer allowing for imaging dynamics of CD4 T cell populations in near real-time.

Importance of CD8 T cell immune responses in viral infections.

CD8 T cells play a major role in antiviral and antifungal immunity and are capable of secreting pro-immune molecules such as interferon-γ, tumor necrosis factor-α, and interleukin-2, and can release cytotoxic granules containing granyzme-B and perforin that help kill infected cells. Pathogen-specific immunity usually develops over a course of weeks following infection. The frequency of these cells in the circulation degrade with time, although they can mount an amnestic response following antigen exposure leading to rapid proliferation and increased effector T cell phenotypes[45]. As a result, they are key players in controlling acute infection and protect from future viral challenge.

Memory T cell responses likely play an important role in SARS-CoV-2 immunity and are likely an essential component of the coordinated immune response following vaccination[46]. Despite lymphopenia in SARS-CoV-1 and SARS-CoV-3, increased frequency of cells responding to various antigens such as Spike, Nucleocapsid, membrane, and accessory (functional) protein (*e.g.* ORF 1ab) peptide sequences develop within the weeks following infection[45,46Grifoni, 2020 #2249]. In addition, mucosal immune responses (*e.g.* tissue resident memory T cells) may also play a crucial role in this response as this is the initial and major site of SARS-CoV-2 infection and replication. Cytotoxic CD8 T cells also play a critical role in controlling acute and chronic untreated HIV infection and important in maintaining viral latency during ART[47,48]. However, these cytolytic CD8 T cells may be excluded from various immune privileged sites, such as B cell follicles containing follicular CD4 T cells, a major component of the HIV reservoir. As a result, there is urgent need for direct PET imaging strategies to characterize the whole-body T cell response in the setting of various infections. Non-invasive modalities have the potential to significantly increase our understanding of immune responses *in vivo*.

Direct immunoPET imaging of CD 8 T cell immune responses.

^{89}Zr-Df-IAB22M2C[49] is a CD8 T cell-specific radiolabeled minibody that allows imaging, tracking and quantification of CD8-expressing T cells *in vivo* by PET imaging as shown in Figure 2. Early phase human studies have demonstrated successful targeting of tumor tissue enriched in CD8 T cells. Therefore, there is clear rationale to pursue direct imaging of CD8 T cell responses using ^{89}Zr-Df-IAB22M2C in the setting of infection. As above, total-body PET imaging has the potential to allow following radiolabeled CD8 T cell turnover at sites of active infection and as they traffic from lymph node stores for several weeks following

injection of tracer[49]. Repeat administration of tracer may also be performed if cumulative radiation dose can kept low in order to examine the temporal and anatomical dynamics and replenishment of CD8 T cells from acute through convalescent infection. There are several distinct advantages of total-body PET for studies of T-cell biology in response to viral and other infection. These include the ability to image with high temporal resolution the distribution throughout the whole body allowing for whole body, quantitative, functional parametric images[30,31], and to capitalize on its geometrical efficiency to image with the highest sensitivity to allow the reconstruction of images with high statistical quality[50] with the potential for delineating, for the first time, T cell activity within the lymphatic system. As a result, there is urgent need for further clinical implementation of CD8 T cell-specific immunoPET strategies in viral diseases such as CVOID-19, HIV, among many others.

PET Imaging T Cell Activation.

Recent advances in molecular imaging have enabled PET imaging of T cell specific immune activation and proliferation. More specifically, the radiofluorinated imaging agent, [^{18}F]F-AraG was synthesized with a goal of development for human use. F-AraG is a fluorinated purine derivative with selective T-cell uptake[51,52]. [^{18}F]F-AraG is a high affinity substrate for deoxyguanosine kinase (dGK) and a low affinity substrate for deoxycytidine kinase (dCK). Both dGK and dCK are over-expressed in activated T cells. Blocking the expression of either dGK or dCK causes reduction in [^{18}F]F-AraG uptake, while over-expression of either dGK or dCK leads to increased accumulation of [^{18}F]F-AraG. [^{18}F]F-AraG PET has been used to investigate immune activation in murine models of various inflammatory disorders, malignancies and allogeneic stem cell transplantation[51–53]. Data from these *in vivo* studies demonstrate that this approach yields highly sensitive imaging of activated T cells. Importantly, [^{18}F]F-AraG was more specific for activated CD8 and CD4 T cells than for monocytes/macrophages. As a result, this novel tracer has a role in imaging CD8 T cell immune responses to infection and our group has several human studies enrolling or in development to study cellular responses to HIV and SARS-CoV-2 infection. However, high sensitivity total-body PET imaging has the potential to greatly enhance the utility of such a tracer.

Summary and Future Development

The development of specific imaging biomarkers of infectious pathogens and immune responses is challenging. Several obstacles of this development, however, may be overcome with high sensitivity total-body PET imaging technologies that allow for improved resolution and dynamic quantification of radiotracer uptake over time. The combination of full field of view and enhanced temporal resolution in total-body PET imaging allows for improved dynamic quantification of radiotracer uptake over time and may enable whole body, non-invasive systems immunology approaches to infectious disease research.

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Key Points

Total-body Positron Emission Tomography (PET) enables very high sensitivity imaging with dramatically improved signal to noise ratio.

Total-body PET can be leveraged to decrease the amount of radiotracer required, thereby permitting more frequent imaging or longer imaging periods during radiotracer decay.

Novel approaches to PET imaging in infectious disease are limited by traditional imaging technologies which may be overcome by total-body PET strategies.

Synopsis

Total-body Positron Emission Tomography (PET) enables very high sensitivity imaging with dramatically improved signal to noise ratio. These enhanced performance characteristics allow for decreased PET scanning times acquiring data “total-body wide” and can be leveraged to decrease the amount of radiotracer required, thereby permitting more frequent imaging or longer imaging periods during radiotracer decay. Novel approaches to PET imaging infectious diseases are emerging, including those that directly visualize pathogens *in vivo* and characterize concomitant immune responses and inflammation. Efforts to develop these imaging approaches are hampered by challenges of traditional imaging platforms which may be overcome by novel total-body PET strategies.

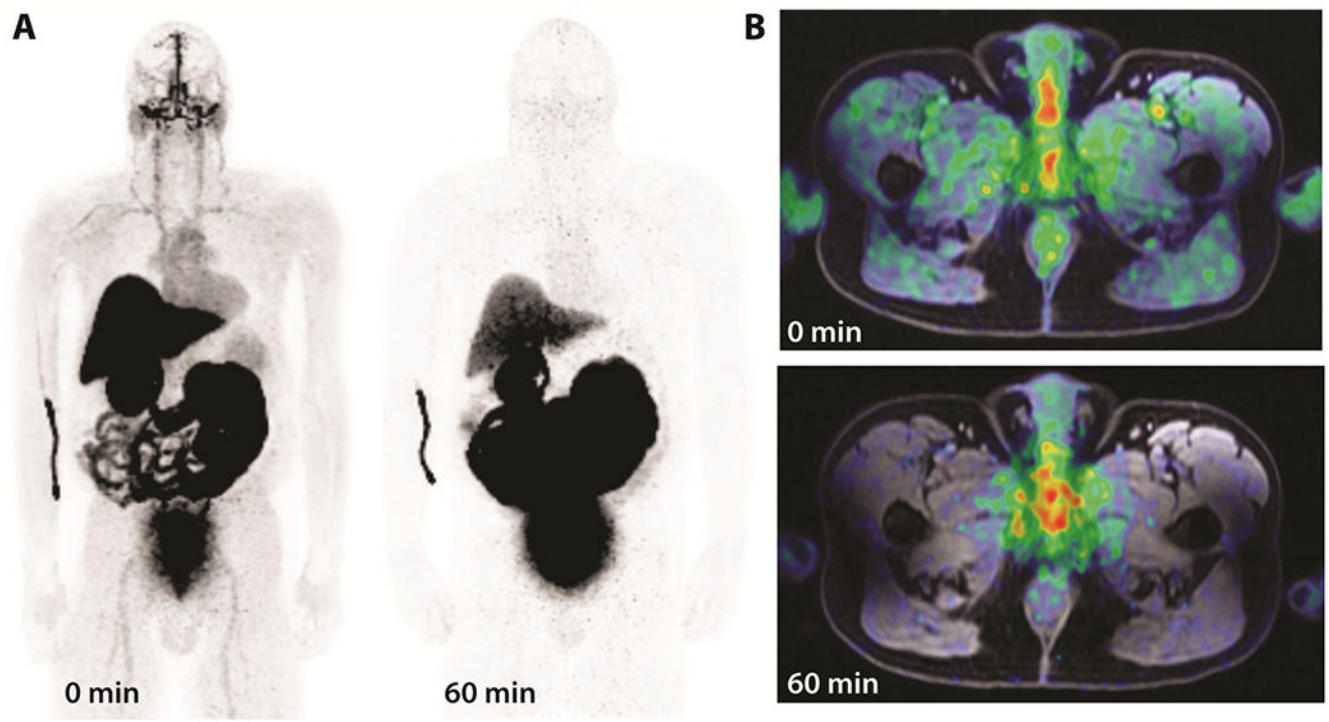

Figure 1.

[^{18}F]Raltegravir PET imaging in a participant with HIV on suppressive ART. Maximum intensity projections acquired immediately and 60 minutes following intravenous injection demonstrate rapid elimination of tracer from tissues that may harbor persistent HIV (**A**). Axial PET-MR overlays of inguinal lymph nodes regions are shown in (**B**). Low tracer uptake was identified in inguinal lymph nodes highlighting the need for high sensitivity total-body PET imaging that will allows for dynamic temporal imaging of antiretroviral tissue distribution and kinetics.

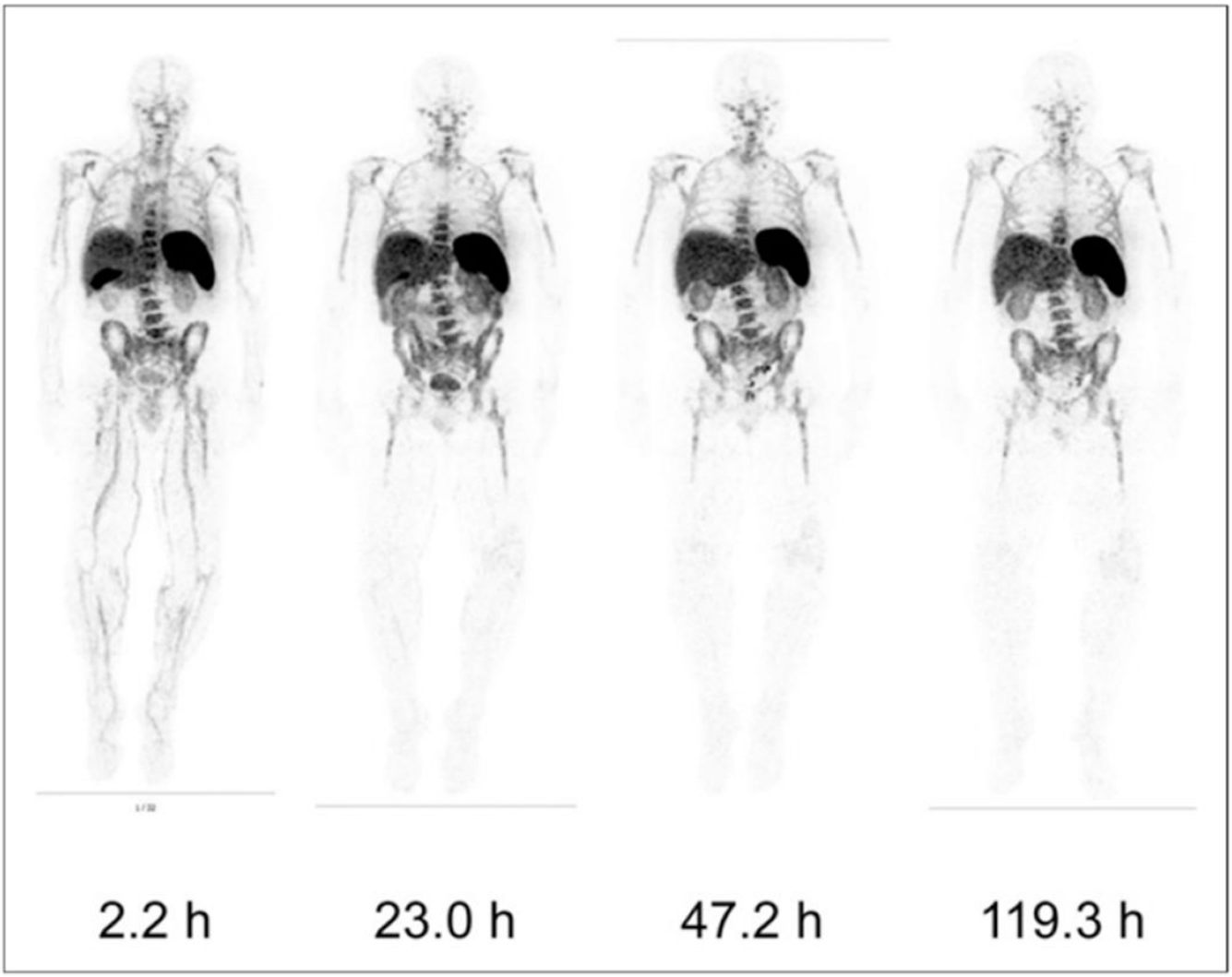

Figure 2.

Biodistribution: Whole-body images of a participant at various times after injection of ^{89}Zr-IAB22M2C (CD8 T cell-specific minibody; 1.5-mg dose). All images show most intense activity within spleen, followed by marrow, liver, and kidneys. Reproduced from Pandit-Taskar *et al.*[49].