Primary immunodeficiency in Africa – a review

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Background. Efforts have been made worldwide to improve awareness and treatment of primary immunodeficiency (PID). This has also gained momentum on the African continent albeit at a slower pace.
Objective. This review reports on the current status of PID on the African continent regarding its prevalence, distribution, genetic mutations and challenges in diagnosis and treatment of affected patients.
Method. We evaluated all studies published from the African continent in the field of PID dealing with prevalence, epidemiology, case reports and genetic findings.
Results. The prevalence of PID on the African continent has been estimated to be as high as 902 631 individuals. PID still is mostly underdiagnosed in Africa and although progress has been made in parts of the continent many challenges still remain regarding awareness, diagnosis, registration and care of these patients.
Conclusion. Given the unique genetic mutations reported in PID patients on the African continent and the feasibility of hematopoietic stem cell transplantation and gene therapy, increased awareness should be encouraged and new therapeutic options considered.

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Primary immunodeficiency disease (PID) comprises a genetically heterogeneous group of disorders caused by defects in components of the immune system. PIDs affect different components of the innate and adaptive immune systems, including neutrophils, macrophages, dendritic cells, complement proteins, natural killer (NK) cells, and T- and B-lymphocytes.[1 2]

Classification

Most PIDs are caused by mutations in single genes but the variable penetrance of these mutations results in diverse phenotypes and severity, which makes recognition and differential diagnosis difficult.[3,4] Owing to this complexity, the International Union of Immunological Societies (IUIS) Expert Committee on Primary Immunodeficiency has developed a classification for PID with the goal of facilitating diagnosis and treatment. According to the last updated report in 2015, PIDs are categorised into nine major groups (Table 1).[5]

Clinical manifestations

Individuals suffering from PIDs are more prone to recurrent and chronic infections with a number of different infectious agents, which cause significant morbidity and mortality. Although impairment of immune function can affect various organs, the most common sites of infection are the sinopulmonary system and the gastrointestinal tract. While unusual organisms generally cause these infections, typical infections that are atypical in length and severity are more often observed and may lead to lethal outcomes. In addition to susceptibility to infections, a poorly regulated immune system in PID patients may lead to inflammation, autoimmunity and malignancy.[2]

Global prevalence of PID

While PIDs are individually quite rare, collectively they represent a significant burden of disease. Recent studies which have extrapolated the prevalence of PID from registry data have shown that the disease may be more common than previously estimated[6-10] and, in fact, it has been suggested that the prevalence and incidence of PIDs may be as high as those observed for diseases such as leukaemia.[6]

To estimate the global prevalence of PID in 2013, Bousfiha *et al.*[6] used data from continental and national registries in specific records from the Australia/New Zealand registry[7] and two specific epidemiological surveys conducted in the USA.[8,9] The prevalence of PIDs in different countries was extrapolated from these registries and surveys based on the populations of each country. It is estimated that as many as 6 million people may be living with a PID worldwide,[6] whereas only 27 000 - 60 000 (0.45 - 1%) have been registered in national registries and the Jeffrey Modell Centers Network (JMCN). Table 2 illustrates the frequency of PID worldwide as estimated in the Bousfiha *et al.*[6] study.

In an attempt to report all PID cases diagnosed worldwide since 2013, the Jeffrey Modell Foundation (JMF) has launched an annual survey in 358 institutions within the JMCN, covering 86 countries on 6 continents. In its latest report in 2018, JMF indicated that 187 988 PID patients were being followed globally. A total of 94 024 were identified as having a specific named PID.[10] According

Table 1. Classification of PID from the IUIS Expert Committee for Primary Immunodeficiency[5]

1	Immunodeficiencies affecting cellular and humoral immunity (e.g. SCID)
2	Combined immunodeficiency with Associated or Syndromic Features (e.g. WAS, ataxia-telangiectasia)
3	Predominantly antibody deficiencies (e.g. agammaglobunaemia)
4	Diseases of immune dysregulation (e.g. Chediak-Higashi syndrome)
5	Congenital defects of phagocyte number function or both (e.g. LAD1)
6	Defects in intrinsic and innate immunity (e.g. MSMD)
7	Autoinflammatory disorders (e.g. familial Mediterranean fever)
8	Complement deficiencies (e.g. complement cascade component deficiencies)
9	Phenocopies of PID (e.g. autoimmune lymphoproliferative syndrome)

PID = primary immunodeficiency; SCID = severe combined immunodeficiency; WAS = Wiskott-Aldrich syndrome; LAD1 = leukocyte adhesion deficiency type 1; MSMD = Mendelian susceptibility to mycobacterial disease.

Table 2. Worldwide frequency of PID estimated by Boushifa *et al.*[6]

Region	Estimate of the number of PID patients based on a prevalence of 5.6/100 000 inhabitants from the Australian Registry[7]	Estimate of the number of PID patients based on a prevalence of 86.3/100 000 inhabitants from the Boyle and Buckley's survey[8]	Estimate of the annual incidence of PID based on an incidence of 10.3/100 000 person years from Joshi *et al.*[9]	Registry
Europe	41 401	638 015	76 148	18 392*
Africa	58 572	902 631	107 730	1 306†
North America	19 464	299 947	35 799	2 804‡
South America	22 214	342 336	40 858	3 321
Asia	235 617	3 631 027	433 367	3 841§
Oceania	2 082	32 082	3 829	1 209¶
Worldwide	390 546	6 018 593	718 326	60 364‖

PID = primary immunodeficiency.
*Europe.
†North Africa.
‡USA.
§Japan and Iran.
¶Australia and New Zealand.
‖2011 JMF registries.

to this report, the subgroup 'predominantly antibody deficiencies' comprising 45% of the PID patients identified is the leading global PID followed by 'combined immunodeficiency with associated or syndromic features' in 13% of patients. This study also showed that some PIDs are more common in certain geographic areas than others.[10]

As seen above, different studies have generated inconsistent results. Moreover, worldwide data registries are not able to provide full coverage of PID patients at the present time. Therefore, the identification of PID patients is confronted by an underreporting bias. Regardless of these challenges, PIDs are clearly more common than generally thought.

Diagnosis

There is a lack of awareness of PIDs among the public and healthcare workers, resulting in delays in diagnosis. On the other hand, an important issue affecting patient outcomes is the time interval between the onset of symptoms and making a diagnosis. Therefore, early diagnosis is critical to prevent significant morbidity and mortality. In order to raise the index of suspicion among healthcare professionals and patients, the medical advisory board of the JMF identified 10 warning signs of PID (http://www.info4pi.org/aboutPI/pdf/General10WarningSignsFINAL.pdf) (Table 3). Knowing these warning signs helps physicians to identify patients suitable for appropriate immunological evaluation.[2,14] The IUIS PID expert committee has also recently developed a phenotypic classification, which through nine algorithms helps clinicians with bedside diagnosis of PIDs.[15] Once an immunodeficiency is suspected, a thorough history and physical examination will further direct the initial workup for screening of the immune system. If the result of the initial evaluation is positive, further testing will be done. The definite diagnosis of a PID which is important for the management of patients and further genetic counseling is reached by molecular diagnosis.[16] However, despite scientific progress in the field, there are still inadequate laboratory resources and diagnostic methods in many countries.[17] In fact, variations observed in the number of cases reported from country to country could often be related to the lack of access to appropriate laboratory testing.[18]

Table 3. Ten warning signs of a PID in children

1	>4 ear infections in one year
2	>2 severe sinus infections in one year
3	>2 months of antibiotic treatment with little effect
4	>2 pneumonias per year
5	Insufficient weight gain or growth delay
6	Recurrent deep skin or organ abscesses (e.g. liver, lungs)
7	Persistent thrush in mouth or fungal infection on skin
8	Need for intravenous antibiotics to clear infections
9	>2 deep seated infections (e.g. septicaemia, meningitis)
10	Family history of a PID

PID = primary immunodeficiency.

Treatment

Most PIDs are chronic diseases and, once recognised, patients require specific care for the rest of their lives. However, the treatment of PID is complex and generally requires both supportive and definitive

approaches carried out by a multidisciplinary team. Initial therapy for most patients is supportive and involves aggressive management of the infection, immunoglobulin (Ig) replacement therapy, and antibiotic and antifungal prophylaxis. Ig replacement therapy has proven to increase the survival rates and decrease the frequency of life-threatening infections, especially pneumonia in antibody-deficient patients.[20-22] According to the 2018 JMF survey, 23 967 patients were receiving Ig therapy worldwide.[10] While cytokine- and enzyme-replacement therapy are other treatment modalities for some of these patients, haematopoietic stem cell transplantation (HSCT) and gene therapy could be considered as the definitive cure for a group of more severe PIDs, such as severe combined immunodeficiency (SCID). [19,23,24]

An allogeneic HSCT involves the intravenous infusion of allogeneic haematopoietic stem cells into the recipient's body usually after preparation of the recipient with a conditioning regimen, which permits some degree of donor cell engraftment and replacement of lymphohaematopoietic function.[26] This procedure was first performed in 1968 on a 22-month-old male infant suffering from SCID.[25] In the past 45 years, there have been great advances in the field of HSCT.[26] The remarkable improvements in allogeneic HSCT, despite the limitations of HSCT, e.g. the lack of human leukocyte antigen (HLA)-compatible donors and also complications such as graft-versus-host disease (GVHD), have increased interest in gene therapy for treating PID patients.[19]

Gene therapy was first introduced in the early 1990s.[28,29] In this approach, a normal copy of the mutated and disease-related gene of the PID patient is introduced into the patient's stem cells *ex vivo* using a viral vector, following which the transduced cells are transplanted back into the patient's body.[19] Given the fact that disease-related genes have now been found for most PIDs, gene therapy may become an important treatment option for many of these conditions. However, gene therapy runs the risk of insertional mutagenesis which is dependent on the nature of the technology used, such as gene editing and the type of vector.[31] In 2018, the JMF reported on the total number of patients worldwide who had received HSCT or gene therapy: 4 421 and 181 patients, respectively.[10]

Methodology

In this review, we evaluated all studies published from the African continent in the field of PID regarding prevalence, epidemiology, case reports and genetic findings. To this end, we performed a literature search in PubMed using the keywords 'prevalence', 'incidence', 'primary immunodeficiency', 'genetic mutations' and 'Africa'. We excluded studies on immunodeficiency due to human immunodeficiency virus (HIV) by using the keyword 'not HIV'. In our search we had no filter regarding the year of publication of the articles. We identified many African studies on different aspects of PID from the northern and southern regions of the continent. We found only one study from western Africa but no studies from eastern or central Africa. However, it should be cautioned that findings from northern and southern Africa cannot necessarily be extrapolated to other regions on the African continent.

Results

When compared with other continents, Africa has experienced a delay with regard to PID diagnosis and care. However, with the establishment of the African Society for Immunodeficiencies (ASID; www.asid.ma) in Casablanca (Morocco) in 2008, there has been an increase in awareness on the continent of PIDs among physicians and the general public. Moreover, ASID has begun to collect data from PID patients for the purpose of creating an international registry. In recent years, different regions of the African continent have also been involved in hosting international congresses and workshops on PID and collaborating with experts from various parts of the world.[32] In fact, the regions of North Africa and the Middle East have joined efforts by hosting 'The Middle East and North Africa Immunodeficiency' (MENAID) meetings; it is hoped that this will help to improve the quality of life of patients with PID. What both regions have in common is their high prevalence of consanguineous marriages (20 - 60%) which results in a higher incidence of autosomal recessive PIDs.[32,33] Another example of a medical society in Africa that is driving the dissemination of medical information and influencing public opinion is the 'Primary Immunodeficiency Diseases South Africa' working group, which is an active Working Group of the Allergy Society of South Africa (ALLSA) and hosts annual congresses and meetings (www.allergysa.org).

Prevalence of PID on the African continent

Very few studies have been conducted in Africa which specifically describe the prevalence and epidemiological features of PIDs on the continent. Those that have been conducted are shown in Table 4.[35-40] In the latest JMF global survey, 1 836 patients with PIDs out of a global total of 94 024 were from Africa.[10] Africa is the second most populous continent, suggesting that it should have a larger number of PID cases, yet its registry contains the smallest proportion of cases. Bousfiha *et al.*[6] estimated the prevalence of PID to be 902 631 cases in Africa. The exact prevalence of PID on the African continent remains unknown.

Barbouche *et al.* [33] investigated the prevalence of PID in northern Africa by collecting data from PID referral clinics in Morocco, Egypt and Tunisia and found that the most prevalent immunodeficiency reported from Egypt and Tunisia was combined immunodeficiency (41% v. 27%), while that from Morocco was combined immunodeficiency with associated or syndromic features (34%). The authors concluded that the hallmark of their North African PID cohort was the high rate of autosomal recessive PIDs compared with the European Registry which is aligned with the high frequency of parental consanguinity in the region.

Novel mutations in the African population

Many studies in the northern region of Africa describe an autosomal recessive transmission mode for PIDs and some have reported novel autosomal recessive gene mutations.[41-60] Due to this fact, the northern region of Africa seems to be a distinctive epidemiological area for the study of genetic diseases, such as PIDs, which has drawn the attention of many researchers in the past decade. Table 5 illustrates some of the studies describing molecular characterisation, novel genetic mutations and founder effects of PIDs undertaken mainly in Africa.

Autosomal recessive PIDs are particularly frequent in North African populations, and a strong founder effect for specific mutations in PIDs has been reported. For example, the major histocompatibility complex (MHC) class II combined immunodeficiency has been described mainly in patients living in or originating from North African countries (predominantly the Maghrebian countries, i.e. Morocco, Algeria and Tunisia). Therefore, it has been considered to be a 'Maghrebian disease'. In fact, several studies have reported a founder effect for the *RFXANK* gene mutation 752delG26 in these patients.[46,48,49,55,59] In 2011, Ouederni *et al.*[55] dated the founder event responsible for this mutation in this population to ~2 250 years ago. A study by Ben-Mustapha *et al.*[44] in 2014 reported a common founder

Table 4. African studies describing the epidemiological features of PIDs on the continent

Study	Location	Duration of study	*N*	Most common PID	Consanguinity	M:F ratio	Mean age at diagnosis	Main presentation at time of diagnosis	Treatments
Reda *et al.*[35]	Pediatric Allergy and Immunology Department, Children's Hospital, Ain Shams University, Cairo (Egypt)	2004 - 2008	64	Predominantly antibody deficiencies (35.9%); combined T and B cell immunodeficiency (29.7%); other well-defined immunodeficiency syndromes (18.7%)	62.5%	1.9:1	29.9 months	Pneumonia	37.5% IVIG 1 bone marrow transplant
Bousfiha *et al.*[36]	Clinical Immunology Unit of Averroes University Hospital Casablanca (Morocco)	1998 - 2012	421	Well-defined syndromes with immunodeficiency (27.4%); Predominantly antibody deficiencies (22.7%); combined Immunodeficiency (20.6%)	43.2%	1.17	6.21 years	LRTIs	Bone marrow transplantation in 10 patients
Bejaoui *et al.*[37]	Centre National de Greffe de Moelle osseuse Bab Saadoun Tunis (Tunisia)	1988 - 1996	152	Combined immunodeficiency (58.5%); Predominant antibody defect (23%)	54%	NG	NG	NG	NG
Mellouli *et al.*[38]	Tunisian Registry of Primary Immunodeficiencies. (Tunisia)	1988 - 2012	710	Combined T-cell and B-cell immunodeficiency disorders (28.6%) congenital defects of phagocytes (25.4%) other well-defined immunodeficiency syndromes (22.7%)	58.2%	1.4:1	24 months	LRTIs	
Eley *et al.*[39]	RCWMCH Immunology Service (SA)	1983 - 1996	93	56% Predominant antibody deficiency	NG	1.5:1	NG	Sinopulmonary infection	NG
Naidoo *et al.*[34]	RCWMCH (SA)	1983 - 2009	168	Antibody deficiencies (51%); well-defined immunodeficiency syndromes (24%); combined B and T cell deficiencies (11%)	1.19%	1.5:1	51 months	URTIs and LRTIs	45% IVIG 2 patients bone marrow transplantation
Esser[40]	South African PID registry	2008 - 2012	200	Antibody deficiencies (45%); complement deficiency (31%); phagocyte defects (6.4%)	30% positive family history but no consanguinity reported	1:1	8 years	Respiratory tract infections	37% IVIG 2 patients bone marrow transplantation

PID = primary immunodeficiency; IVIG = intravenous immunoglobulin; LRTI = lower respiratory tract infection; NG = not given; RCWMCH = Red Cross War Memorial Children's Hospital; SA = South Africa, URTI = upper respiratory tract infection.

Table 5. Genetic studies on PID in Africa and elsewhere

Study	Country where study was undertaken	Patient number and origin	PID studied	Genetic findings
Studies indigenous to Africa				
Glanzmann *et al.*[71] (2018)	SA	1 SA family	MSMD	*De novo* heterozygous 4 bp deletion in exon 6 of *IFN-γR1* at nucleotide 818 (818del4)
Glanzmann *et al.*[72] (2017)	SA	1 SA family	Aicardi-Goutières syndrome	Homozygous c.1681_1682delAG; p. Ser561Phefs*61 mutation in exon 15 of *SAMHD1*
Schlechter *et al.*[73] (2017)	SA	1 SA family	Recessive atypical combined immunodeficiency	Homozygous c.G1033A p.Val345Met nucleotide variant situated in exon 5 of *MAP3K14*
Kinnear *et al.*[74] (2017)	SA	1 Somalian family	THE-S	Homozygous mutation (c.4507C>T rs200067423) in *TTC37*
Glanzmann *et al.*[75] (2017)	SA	1 SA family	Immunodeficiency with autoimmunity	Compound heterozygous variant in *LRBA* (NM_006726) (c 3296 C>G and c.3407 C>T).
Owen[41] (2015)	SA	7 SA families	Complement deficiency	Complement *C5* gene mutation c.754G>A:p.A252T; common in the Western Cape
Jlajla[42] (2014)	Tunisia	1 Tunisian family	C1q deficiency	Novel g.5580G4C mutation
Sassi *et al.* [43] (2014)	Tunisia	6 patients from 2 Tunisian families	Hyper IgE syndrome	Novel homozygous mutations in PGM3 in 2 Tunisian families
Ben-Mustapha[44] (2014)	Tunisia	6 Tunisian patients	MSMD	Founder effect for the c.298_305del mutation in the *IL12B* gene
Baba[45] (2014)	Morocco	12	CGD	Four different mutations of *CYBB*, a recurrent mutation of *NCF1* and a new mutation of *NCF2* in three patients
Ben-Mustapha *et al.* [46] (2013)	Tunisia	34 (belonging to 28 Tunisian families)	MHC class II expression deficiency	Founder effect for the c.338-25_338del26 mutation in the *RFXANK* gene in 25 patients
Landouré *et al.*[47] (2013)	Mali	3 patients from 1 Malian family	Ataxia-telangiectasia	Novel c.7985T > A mutation in *ATM* gene
Djidjik *et al.* [48] (2012)	Algeria	11 Algerian patients	MHC class II expression deficiency	Founder effect for the 752delG26 mutation in *RFXANK* gene in 9 patients
Naamane *et al.* [49] (2010)	Morocco	10 Moroccan patients	MHC class II expression deficiency	Founder effect for the 752delG26 mutation in the *RFXANK* gene in 10 patients
El Kares *et al.*[50] (2006)	Tunisia	15 Tunisian patients	CGD	Two novel and recurrent mutations in *NCF2* and *CYBA* gene
Pienaar *et al.*[51] (2003)	SA	2 SA patients	Hyper IgM	First report of X-linked hyper IgM (HIGM1) from SA
Elloumi-Zghal *et al.* [52] (2002)	Tunisia	5 Tunisian patients	MSMD	*IL-12Rb1* gene mutation in 2 patients and *IL-12p40* gene mutation in 3 patients; first description of familial cytokine deficiency
Eley BS *et al.* [53] (2001)	SA	5 SA patients	SCID	3 with IL-2RγC deficiency; 1 with RAG1 deficiency 1 with IL-7Rα deficiency
Pienaar *et al.*[54] (2000)	SA	5 SA patients	X-linked agammaglobulinaemia	*Btk* gene mutation

...continued

Table 5. (continued) Genetic studies on PID in Africa and elsewhere

Study	Country where study was undertaken	Patient number and origin	PID studied	Genetic findings
Studies from outside Africa				
Ouederni *et al.*[55] (2011)	France	35 North African patients	MHC class II expression deficiency	Founder effect for the 752delG26 mutation in the *RFXANK* gene in 35 patients
Boisson-Dupuis[56] (2011)	France	50 patients from Morocco, Iran and Turkey	MSMD	Homozygosity for loss-of-function *IL12RB1* alleles in 2 patients, 1 from Morocco and the other from Iran
Lennon-Duménil *et al.*[57] (2001)	France	1 North African patient	MHC class II expression deficiency	Uncoordinated expression of the *HLA-D* genes in a new *RFXANK* gene mutation
Altare *et al.* [58] (2001)	France	2 siblings from North Africa	MSMD	Heterogeneity of the clinical phenotype associated with IL-12RB1 deficiency
Wiszniewski *et al.*[59] (2000)	France	20 North African patients	MHC class II expression deficiency	Founder effect for the 752delG26 mutation in the *RFXANK* gene in 17 patients
Jouanguy *et al.*[60] (1996)	France	1 Tunisian patient	MSMD	First report of INFγ receptor deficiency

PID = primary immunodeficiency; SA = South Africa; INFγ = interferon gamma; *SAMHD1* = SAM and HD domain containing deoxynucleoside triphosphate triphosphohydrolase 1; *MAP3K14* = mitogen-activated protein kinase kinase kinase 14; THE-S = thrichohepatoenteric syndrome; *LRBA* = LPS responsive beige-like anchor protein; MSMD = Mendelian susceptibility to mycobacterial infection; C1q = serum complement subcomponent C1q; IgE = immunoglobulin E; PGM3 = phosphoglucomutase 3; IL = interleukin; CGD = chronic granulomatous disease; *CYBB* = cytochrome B-245 beta chain; *NCF* = neutrophil cytosolic factor 1; MHC = major histocompatibility complex; *RFXANK* = regulatory Factor X-associated ankyrin-containing protein; *CYBA* = cytochrome B-245 alpha chain; IgM = immunoglobulin M; RAG1 = recombination activating 1; *Btk* = bruton tyrosine kinase; *HLA* = human leukocyte antigen.

mutation for Mendelian susceptibility to mycobacterial disease (MSMD) arising ~1 100 years ago.

There are additional scattered studies from the region describing PID, including patients' susceptibilities to various infections and case reports.[61-68]

Diagnosis of PID on the African continent

Although basic laboratory tests are available for the diagnosis of PID in some African countries, there are still limitations with regard to specialised immunological and genetic tools required for more accurate investigations. Particular laboratory tests, e.g. specific antibodies (IgG subclasses) lymphocyte subpopulations and proliferation studies, and functional phagocyte tests, are only available in a very limited number of referral centres.

With respect to molecular studies, many centres on the continent are in the early phases of development, with limited capacity for genetic diagnosis of some PIDs. There has been a recent drive in African referral centres to expand molecular diagnostic services for PID, which includes polymerase chain reaction (PCR) analysis of T-cell receptor excision circles (TREC) and Kappa-deleting recombination excision circles (KREC) as part of a newborn screening programme for severe PIDs. Still, most centres work in collaboration with specialised laboratories abroad for occasional definitive diagnosis of selected PID cases.

In 2016, a private diagnostic laboratory in South Africa developed a targeted next-generation sequencing (NGS) gene panel consisting of 99 of the most frequently associated PID genes.[70] The panel can be used as both a molecular confirmation and a screening tool for 18 PID phenotypes found within the nine International Union of Immunological Societies (IUIS) PID classifications (Table 1). Furthermore, whole exome and transcriptome sequencing are currently being investigated for those more challenging cases in which clinical presentation is indicative of a PID when immunological investigations and targeted sequencing have proved uninformative. Table 6 shows the laboratory tests available for the diagnosis of PID in SA; these have been grouped into a stepwise investigative approach. All the tests indicated are available in SA and the public (government) sector has permission to refer this work to Ampath through the National Health Laboratory Services when clinically indicated. Lack of diagnostic facilities can cause delays in diagnosis and may ultimately compromise the clinical outcome of these patients.[33,34,36]

Treatment options for PID in Africa

With an average mortality rate of 20% in northern and southern Africa, there are still considerable challenges in the region regarding the management and overall clinical outcome of PID patients.[34-37] Generally, 40% of PID patients in these regions receive intravenous immunoglobulin (IVIG)[34,35,40] despite limitations in the availability of IVIG in some regions.[33]

HSCT using haploidentical donors has been introduced as a treatment option in severe cases of PID but only in very few centres on the continent and with long waiting lists.[34-36] However, due to the cost morbidity and mortality associated with HSCT, clinicians are very cautious about administering gene therapy, specifically if the patient is fairly well controlled.

Gene therapy as an option in the African continent

According to the JMF global survey, there has been a significant increase in the number of patients receiving gene therapy worldwide, with the greatest number residing in Western Europe.[10] Although in 2016 the first retroviral long terminal repeat (LTR)-based vector received license for *ex vivo* gene therapy in SCID, many challenges still need to be overcome before gene therapy can be offered as a standard therapy for all patients.[76] To our knowledge, no centre on the African continent has performed gene therapy on PID patients to date. As the field of PIDs continues to grow and the number of children and adults diagnosed with PID in the region increases, gene therapy could become an effective treatment option for patients on the African continent in the future.

Table 6. A stepwise approach to the laboratory diagnosis of PID*

	Test	Association
First-line investigations	Exclude HIV	
	Assessment for atopy	As indicated on history
	Full blood count	Lymphopaenia is an important indicator of possible SCID
	• Differential count for neutrophil and lymphocyte numbers	Small platelets seen in WAS
	• Platelet count and morphology	
	• Serum Ig: G, M, A and E	IgE should be tested in patients who may be at risk of hyper IgE syndrome
	• TRECs and KREC PCR	Used for neonatal screening for SCID and XLA on blood monospots – useful to do prior to giving live vaccines at birth
	• CF screening	Suspected on history and clinical examination
Second-line investigations	IgG subclasses	IgG subclass deficiency and other immunodeficiencies
	Specific antibody response	Indicated with recurrent bacterial infections even in the presence of normal immunoglobulins. Patients have to be off immunoglobulin replacement therapy for 6 months. If these antibody levels are decreased, the patient should be revaccinated and antibody responses should be repeated 4 weeks after vaccine boosting to determine an appropriate increase in specific antibody responses. Note that an unconjugated pneumococcal vaccine, e.g. Pneumovax, should be given to determine an appropriate polysaccharide antigen response.
	• *Pneumococcus* and *Haemophilus influenzae* (targeted to polysaccharide-specific antigens)	
	• Tetanus, diphtheria and *H. influenzae* (target protein antigens)	
	Lymphocyte subsets	Absent in XLA where all immunoglobulin isotypes are severely reduced
	• B cell numbers (CD19)	
	T cell numbers (CD3)	Reduced in T cell defects combined immunodeficiencies and occasionally CVID
	T helper (CD4) and T suppressor (CD8)	
	NK cells (CD16 and CD56)	Isolated NK-cell deficiencies may be associated with recurrent herpes virus infections
	Neutrophil function	
	• Neutrophil oxidative burst	CGD
Third-line investigations	Lymphocyte proliferation studies	T cell deficiencies including SCID, chronic mucocutaneous candidiasis
	• Response to mitogens e.g. phytohaemagglutinin PMA PMA +ionomycin anti-CD3 anti-CD3+IL2	
	• Response to recall antigens e.g. *Candida*, tetanus, varicella-zoster virus	
	Neutrophil antibodies	Alloimmune and autoimmune neutropaenia
	T cell maturation panel: Naïve and memory T cells	Diagnosis of SCID and combined T cell defects
	Recent thymic emigrants (T cells)	Very low in SCID Can be used to monitor bone marrow regeneration post transplant
	Memory B cells	Memory B cells categorise subsets of CVID patients and are decreased in X-linked HIGM
	Alpha/beta/ gamma/delta T cell receptor type	Abnormal in leaky SCID, hypomorphic SCID T cell defects with oligoclonality
	Total haemolytic complement	Complement deficiencies
	• Classic	Patient may suffer from recurrent URTIs and may have a higher risk for severe meningococcal or pneumococcal infections.
	• Alternative	
	Mannan binding lectin (MBL)	
Fourth-line investigations	• Genetic testing	Various PID panels available or exome sequencing as clinically indicated
	• Complement studies	To be discussed with clinical immunologist
	• Confirmatory test	

PID = primary immunodeficiency; HIV = human immunodeficiency virus; SCID = severe combined immunodeficiency; WAS = Wiskott-Aldrich syndrome; Ig = immunoglobulin; TREC = T cell receptor excision circles; KREC = Kappa receptor excision circles; PCR = polymerase chain reaction; XLA = X-linked agammaglobulinaemia; CF = cystic fibrosis; CD3 = cluster of differentiation 3; CVID = common variable immune deficiency; NK = natural killer; CGD = chronic granulomatous disease; PMA = phorbol myristate acetate; IL = interleukin; URTIs = upper respiratory tract infections; MBL = mannan-binding lectin.
*Adapted from Suchard *et al.*[77]

In addition to the outcomes and efficacy of this form of treatment, elevated costs are a major concern. However, many believe that a one-time cure could still save money in the long-term by reducing the need for expensive care. In 2014, Buckland *et al.* [69] reported that the cost of an allogeneic bone marrow transplant for a patient with a primary immunodeficiency was ≥£250 000. In contrast, the manufacture of autologous gene modified $CD34^+$ cells could be achieved at a cost of ~£15 000 - £30 000. The additional follow-up costs after gene therapy treatment for PIDs are also likely to be significantly less given that the length of hospital stay and long-term prophylactic medication requirements and other post-therapy complications are considerably reduced, compared with conventional HSCT.

Limitations regarding PID on the African continent

PID is mostly underdiagnosed in Africa and, although considerable progress has been achieved in parts of the continent, many challenges remain regarding awareness, diagnosis, registration and care of these patients.

At present, only 2 of the 54 countries on the continent have national registries: the Moroccan Society for PID (MSPID, www.pid-moroccansociety.org) and the South African National PID Registry (https://www.pinsa.org.za/). Without national registries, accurate prevalence and incidence data cannot be gathered. Participation in these networks will establish earlier diagnosis and improve treatment and clinical care, resulting in an improvement in the quality of life of these patients. There is also a need to improve public health policy in this field.[6,33]

The lack of specialised physicians in the field of clinical immunology in many areas of the African continent negatively affects the management of PID patients in the region. The training of expert clinical immunologists could assist in raising awareness of PID in the medical community. In addition, networks such as Primary Immunodeficiency Diseases Network of South Africa (PINSA) and ASID could play an important role in creating awareness of PIDs on the continent.

The burden of HIV and other epidemic illnesses, particularly in the sub-Saharan region, is likely to be a major contributor to the under-diagnosis of PID.[28] It is assumed that the expanding HIV epidemic, especially in SA, over the past 30 years has compromised clinical recognition of PID.[34]

In addition to efforts aimed at increasing the awareness of PID in the region, there is a need for improvement in diagnosis. Conducting molecular and genetic studies in the region could support the future development of genetic counseling, prenatal diagnosis and gene therapy.[33]

Africa faces a number of challenges, which include a paucity of diagnostic facilities, limited expertise, as well as limited financial resources. These challenges may be overcome by creating diagnostic referral centers for PID on the continent. These specialised centres could potentially offer basic as well as definitive molecular diagnostic services at a lower cost and faster turnaround time than when samples are sent to international laboratories.

Conclusion

With the exception of South and northern Africa, there appears to be limited activity in the field of PID on the African continent, resulting in lack of awareness, underdiagnoses, mismanagement and suboptimal care. Additionally, as the field of PID is continually growing, advanced therapeutic modalities are rapidly expanding worldwide and options such as gene therapy are becoming a reality. Given the unique genetic mutations reported in PID patients on the African continent and the feasibility of HSCT and gene therapy, these new therapeutic options should be considered.

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