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SYSTEMATIC REVIEW

Influence of Malnutrition on the Pharmacokinetics of Drugs Used in the Treatment of Poverty-Related Diseases: A Systematic Review

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Abstract

Background Patients affected by poverty-related infectious diseases (PRDs) are disproportionally affected by malnutrition. To optimize treatment of patients affected by PRDs, we aimed to assess the influence of malnutrition associated with PRDs on drug pharmacokinetics, by way of a systematic review.

Methods A systematic review was performed on the effects of malnourishment on the pharmacokinetics of drugs to treat PRDs, including HIV, tuberculosis, malaria, and neglected tropical diseases.

Results In 21/29 PRD drugs included in this review, pharmacokinetics were affected by malnutrition. Effects were heterogeneous, but trends were observed for specific classes of drugs and different types and degrees of malnutrition. Bioavailability of lumefantrine, sulfadoxine, pyrimethamine, lopinavir, and efavirenz was decreased in severely malnourished patients, but increased for the P-glycoprotein substrates abacavir, saquinavir, nevirapine, and ivermectin. Distribution volume was decreased for the lipophilic drugs isoniazid, chloroquine, and nevirapine, and the α1-acid glycoprotein-bound drugs quinine, rifabutin, and saquinavir. Distribution volume was increased for the hydrophilic drug streptomycin and the albumin-bound drugs rifampicin, lopinavir, and efavirenz. Drug elimination was decreased for isoniazid, chloroquine, quinine, zidovudine, saquinavir, and streptomycin, but increased for the albumin-bound drugs quinine, chloroquine, rifampicin, lopinavir, efavirenz, and ethambutol. Clinically relevant effects were mainly observed in severely malnourished and kwashiorkor patients.

Conclusions Malnutrition-related effects on pharmacokinetics potentially affect treatment response, particularly for severe malnutrition or kwashiorkor. However, pharmacokinetic knowledge is lacking for specific populations, especially patients with neglected tropical diseases and severe malnutrition. To optimize treatment in these neglected subpopulations, adequate pharmacokinetic studies are needed, including severely malnourished or kwashiorkor patients.

1 Introduction

Malnutrition, defined here as lack of protein and/or calorie intake, is a major public health problem, especially in low-income countries where malnutrition is associated with

Key Points

Malnutrition leads to physiological alterations that affect drug pharmacokinetics.

Patients affected by poverty-related diseases are a highly vulnerable population, requiring optimal and individualized drug treatment.

This systematic review highlights the key findings of pharmacokinetic drug alterations by malnutrition, for specific drug classes and patient populations.

This overview can be used as a basis to predict the effects of malnutrition on the drug pharmacokinetics of poverty-related infectious diseases.

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about 50% of the 10.8 million deaths per year in children under 5 years of age [1–4]. Because of poor hygienic conditions and a lack of access to healthcare, a large proportion of this population is affected by poverty-related infectious diseases (PRDs), including HIV, tuberculosis (TB), malaria, and neglected tropical diseases (NTDs) as defined by the World Health Organization (WHO) [5]. To illustrate, 42% of African children [6] and 43% of Ethiopian adults [7] with HIV were affected by malnutrition. Similarly, 57% of Ethiopian TB patients [8] and 75% of Sudanese children affected by malaria [9] were malnourished. The association between malnutrition and PRDs is bidirectional, where on the one hand malnutrition increases the susceptibility to infections as a result of secondary immune deficiency, and on the other hand, infections can add to the development of malnutrition because of the increased need for anabolic energy by the prolonged activated immune system, and because of complications such as chronic diarrhoea, cachexia, and anaemia [10–12]. An association between NTDs and underweight was found in African children under 5 years of age [13], and, similarly, a negative correlation between malaria parasite density and malnutrition was found in Cameroonian children [14].

Malnutrition can manifest in various forms, depending on the type and severity of protein and calorie deficiency. Kwashiorkor is predominantly characterized by protein deficiency and comes with different clinical signs, including oedema, fatty liver, and anaemia. Marasmus reflects an overall deficiency of energy, mainly characterized by muscular wasting and loss of subcutaneous fat. Although there is still no consensus about the clinical definition of these phenotypes, the differences in biological features have been well described [15]. In children, stunting is usually a result of long-term nutritional deprivation, causing gut mucosal changes and altered levels of drug-metabolizing enzymes, whereas wasting is an acute condition, characterized by insufficient food intake or a high incidence of infectious diseases, and is associated with not only fatty liver but also impaired functioning of the immune system [16, 17].

The different pathophysiological conditions in malnutrition can alter the pharmacokinetics of drugs. Gastrointestinal changes include hypochlorhydria, delayed gastrointestinal emptying time, increased or decreased intestinal transit time, gastric and mucosal atrophy and dysfunction, gastrointestinal inflammation, and pancreatic insufficiency [18–20]. Moreover, in the enterocytes, P-glycoprotein activity is decreased and tight junctions are enlarged, influencing the uptake of nutrients and drugs [21]. Total body water is increased, and adipose mass and lean body mass is reduced, especially in children with marasmus and marasmic-kwashiorkor [20], and kwashiorkor is associated with the presence of oedema [22]. Furthermore, hypoproteinaemia is a common feature of malnutrition [20]. Hypoalbuminaemia is more severe in kwashiorkor than marasmus, and is associated with malnutrition combined with infectious or non-infectious inflammation, likely caused by the increased capillary permeability in inflammation, and a higher albumin degradation rate in the liver [23]. The synthesis of acute-phase proteins such as α1-acid glycoprotein is often increased in malnutrition, although this is related to the inflammation caused by infections, which often accompanies malnutrition [24–26]. In the liver, the basal metabolic rate is reduced with impaired synthesis of protein, and fat accumulation occurs, particularly in kwashiorkor [19]. In severe protein energy malnutrition or kwashiorkor, glomerular filtration rate (GFR) and renal blood flow are diminished, particularly in the presence of dehydration [20], and tubular excretion and reabsorption may be impaired [18]. These physiological alterations can alter the pharmacokinetics of drugs in different ways, which can lead to either reduced treatment efficacy in case of subtherapeutic drug levels, or toxicity in case of overdosing.

An understanding of the effect of different types of malnutrition on pharmacokinetic processes is needed to characterize drug exposure in all patients affected by PRDs, and to improve treatment and dosing guidelines in this vulnerable population. A previous general review found heterogeneous effects of protein-energy malnutrition (PEM) on pharmacokinetics in children and concluded that studies should take into account the differential effects of different forms of malnutrition on drug pharmacokinetics [27]. To provide a complete and systematic overview of the influence of malnutrition on PRD drug pharmacokinetics, we performed a systematic review of published literature on this topic. We aimed to characterize the effects of different types of malnutrition on different pharmacokinetic processes, and if mentioned by the included studies, the potential clinical relevance and whether dose recommendations are necessary for malnourished PRD patients. Furthermore we aimed to identify gaps of knowledge in specific populations.

2 Methods

2.1 Search Strategy

A systematic literature review was performed by a medical information specialist, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [28]. A full literature search was performed on 19 October 2020 in the MEDLINE (PubMed), Embase (OVID), and SCOPUS databases. Publications were searched on a combination of three following free-text words and related standardized

keywords (Medical Subject Heading [MeSH] and Emtree terms): malnutrition, PRDs, and pharmacokinetics. Malnutrition is defined as PEM, including kwashiorkor and marasmus. PRDs include HIV, TB, malaria, and NTDs, as defined by the WHO [5]. NTDs include Buruli ulcer, Chagas disease, Dengue and Chikungunya, Dracunculiasis (guinea-worm disease), Echinococcosis, Foodborne trematodiases, Human African trypanosomiasis (sleeping sickness), Leishmaniasis, Leprosy (Hansen's disease), Lymphatic filariasis, Mycetoma, chromoblastomycosis and other deep mycoses, Onchocerciasis (river blindness), Rabies, Scabies and other ectoparasites, Schistosomiasis, Soil-transmitted helminthiases, Snakebite envenoming, Taeniasis/Cysticercosis, Trachoma, Yaws (Endemic treponematoses), and Zika. Pharmacokinetics include any parameters describing drug exposure, bioavailability, absorption, distribution, protein binding, clearance, or elimination half-life. No limits were applied for date, study design or language. The full search strategy is shown in Table S1 in the electronic supplementary material. Duplicate articles were removed according to the method of Bramer et al. [29].

2.2 Study Selection

Studies were screened and included by two independent reviewers (LV and TD) through each phase of the review. Rayyan QCRI [30] was used to screen references on title and abstract. Studies were included when the studied population included malnourished patients at risk for or affected by one or more PRDs, as well as nonmalnourished patients or healthy volunteers. Although the scope of this review was to compare pharmacokinetics between malnourished and well-nourished infected patients, studies including non-infected patients or healthy individuals as controls were also included due to the overall scarcity of studies with infected patients as controls. Second, studies were included when the pharmacokinetics of drugs intended to treat PRDs in both populations was reported. Studies were excluded when one or more of these criteria were not met. Other exclusion criteria were missing abstract or full-text, nonclinical research, and wrong publication type (i.e. case reports, reviews, or any article not reporting original research). The reviewers resolved discrepancies by consensus. Secondary sources were identified through the reference lists of the included studies.

2.3 Data Extraction

Information from the included studies was extracted and summarized, including PRDs, PRD drugs used for pharmacokinetic analysis, route of administration of these drugs, number of patients, type of malnourished patients, classification of malnutrition as defined by the original study, definition of the control group, patient age range, and country. The methodology of pharmacokinetic analysis was reported, including (1) noncompartmental analysis when concentration time points were compared, maximum concentration (C_{max}) and time to reach C_{max} (T_{max}) were derived by visual inspection of the data, area under the curve (AUC) was calculated by the trapezoidal rule, and/or half-life ($T_{½}$) was derived by linear regression of the last data points; and (2) compartmental analysis, including a standard two-stage approach or population approach. Collected pharmacokinetic parameters for exposure included AUC, concentration on different time points after treatment (C_t), C_{max}, and trough concentration (C_{trough}); drug absorption was characterized by bioavailability; drug absorption rate was characterized by T_{max}, absorption rate constant, and absorption lag time; drug distribution was characterized by apparent central or peripheral volume of distribution and apparent intercompartmental clearance; drug clearance was characterized by apparent clearance, elimination half-life, and elimination rate constant; drug metabolism was characterized by drug/metabolite ratio; and protein binding was characterized by free fraction in plasma, maximum enzyme binding rate, and drug concentration where enzyme achieves half maximum velocity (V_{max}). Results were summarized as the change in any of the pharmacokinetic parameters in the malnourished population compared with those of a nonmalnourished control population.

2.4 Summary and Interpretation of the Results

In order to summarize the findings and interpret the results of the heterogeneous studies, a selection of the main findings was summarized by the reviewers according to the different pharmacokinetic processes (absorption, distribution, metabolism, and elimination). The main findings were summarized per studied drug, and the effects on pharmacokinetics were attempted to relate to mechanistic explanations based on explanations by the original studies or based on other relevant literature. This includes the type and severity of malnutrition, as well as specific drug characteristics (e.g. lipophilicity, P-glycoprotein binding, plasma protein binding, route of elimination). Malnutrition was considered severe when the original study defined patients as severely malnourished or severely wasted, or when patients had a *Z*-score for any of the used body size/mass descriptors of less than or equal to − 3. Other definitions of malnutrition were considered as moderate malnutrition. The different pathophysiological processes in malnutrition associated with pharmacokinetic changes observed for specific drugs were summarized, and when observed for a specific type of malnutrition, this was specified. In the summarizing figure,

the effects on pharmacokinetics were categorized as weak or strong by the reviewers, based on the level of evidence. The evidence for the effect was considered strong when identified by multiple studies, or when the quality of the results of the original study was high (i.e. when the difference between patients and controls was adequately assessed, when pharmacokinetic parameters were adequately and precisely identified). The evidence for the effect was considered weak when the study design to identify an effect was considered poor, when the definition of the malnourished patient and control group was unclear, when the effect was statistically nonsignificant, when contradicting effects were found by different studies, or when other studies could not replicate the results.

3 Results and Discussion

3.1 Publications

The systematic search yielded 1929 abstracts after deduplication (Fig. 1). Screening of the abstracts left 44 publications for inclusion. Five additional publications were identified through reference screening of the included publications. In total, 49 publications were included in this review. The studies were mainly conducted in TB patients (24), HIV patients (12), and malaria patients (11). Only two studies were conducted in patients with an NTD, i.e. helminthiasis caused by *Trichuris trichiura* and visceral leishmaniasis.

3.2 Study Population and Methodology

Overall, the majority of studies were conducted in children (19/24 in TB, 8/12 in HIV, 9/11 in malaria, and 2/2 in NTDs) (Tables 1, 2, 3 and 4). All studies were performed in malnourished patients, with well-nourished patients or well-nourished noninfected volunteers as control subjects. In 2/24 TB studies [31, 32] and 2/12 HIV studies [33, 34], the same patients served as control after nutritional rehabilitation. Malnourished patients had different degrees and forms of malnutrition (moderately or severely malnourished, underweight, wasted, stunted, marasmus, or kwashiorkor), measured by different metrics (see Sect. 3.3). Pharmacokinetic analysis was mostly performed by noncompartmental analysis (20/24 studies in TB, 6/12 studies in HIV, 7/11 studies in malaria, and 1/2 studies in NTDs) (Tables 5, 6, 7 and 8).

3.3 Classification of Malnutrition

The classification of malnutrition in the included studies was very heterogeneous. In the majority of studies, *Z*-score was used to classify the degree of malnutrition (Tables 1, 2, 3 and 4), i.e. the difference in terms of standard deviations from a median nutritional status reference value as defined,

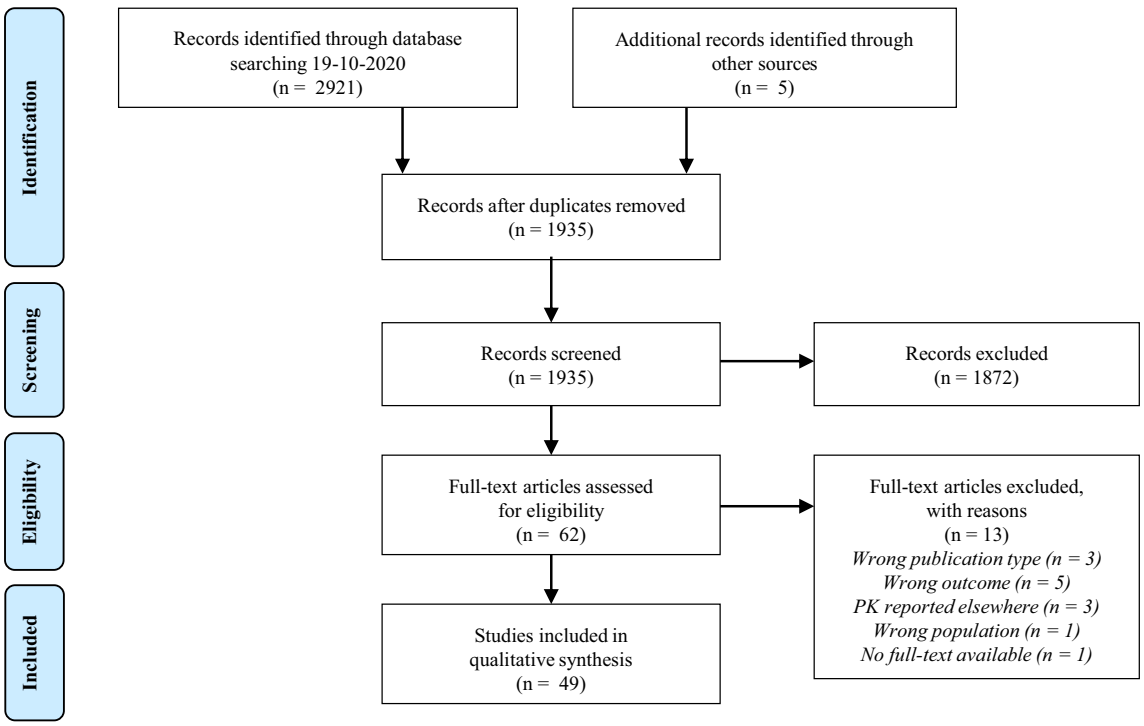

Fig. 1 PRISMA flow diagram. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses, *PK* pharmacokinetics

Table 1 Overview of the included studies in TB patients

Author (year) [Ref]	Drug	Route of administration	Total no. of patients	Malnourished patients (*n*)	Control group (*n*)[a]	Classification malnutrition	Age, years[b]	Country
Buchanan et al. (1979) [31]	Isoniazid	IV	7	Kwashiorkor (7)	Same patients after 21 days (7)	Wellcome classification	1.53 ± 0.79	Pakistan
Polasa et al. (1984) [59]	Rifampicin	PO	28	Uninfected volunteers (8)	Well-nourished uninfected volunteers (10)	AI < 0.18	49	India
	Rifampicin	PO		Patients receiving rifampicin therapy (10)				
Prasad and Krishnaswamy (1978) [75]	Streptomycin	IM	34	(15)	(6)	AI < 0.18	(25–35)	India
Bolme et al. (1988) [54]	Streptomycin	IM	56	Underweight (6); marasmic (6); kwashiorkor (3)	(4)	Wellcome classification	4.9 (0.5–12)	Ethiopia
	Streptomycin	IM		Underweight (11); marasmic (12); kwashiorkor (5)	(9)			
Eriksson et al. (1988)[c] [67]	Isoniazid	PO	41	Underweight (9); marasmic (15); kwashiorkor (6)	(11)	Wellcome classification	(0.5–12)	Ethiopia
Garg et al. (1988) [65]	Isoniazid	PO	63	Malnourished (10)	(13)	AI < 0.18	45 ± 5.2 (40–50)	India
	Rifampicin	PO		Malnourished (10)	(11)			
	Isoniazid and rifampicin	PO		Malnourished (10)	(9)			
Seth et al. (1992)[d] [18]	Rifampicin	PO	115	Undernourished (30); malnourished (10)	(15)	Grade I and II: undernourished; grade III and IV: malnourished	Children	India
	Isoniazid	PO		Undernourished (30); malnourished (10)	(20)			
Seifart et al. (1995) [32]	Isoniazid	PO	13	PEM [no marasmus or kwashiorkor] (13), mean MUAC 135 mm	Same patients after 6 months (13), mean MUAC 150 mm	Weight, weight-for-age, and MUAC scores	2.3 (0.8–7.6)	South Africa
Graham et al. (2006) [88]	Pyrazinamide	PO	34	Undernourished (12); marasmic (9)	(6)	Wellcome classification	5.6	Malawi
	Ethambutol	PO		Undernourished (3); marasmic (1)	(3)			
McIlleron et al. (2009) [82]	Isoniazid	PO	56	Kwashiorkor (NA)	(NA)	Clinical diagnosis and presence of edema	3.22 (0.25–13)	South Africa
Roy et al. (2010) [66]	Isoniazid	PO	20	Moderately malnourished (NA)	(NA)	WAZ less than −2 and greater than −3	(5–12)	India

Table 1 (continued)

Author (year) [Ref]	Drug	Route of administration	Total no. of patients	Malnourished patients (*n*)	Control group (*n*)[a]	Classification malnutrition	Age, years[b]	Country
Verhagen et al. (2012) [78]	Isoniazid, rifampicin, and pyrazinamide	PO	30	Malnourished patients (4)	(26)	<5 years of age: WAZ or HAZ less than −2; >5 years of age: BAZ less than −2	(1–15)	Venezuela
Ramachandran et al. (2013) [77]	Isoniazid, rifampicin, and pyrazinamide	PO	84	Stunting (22); underweight (31); wasting (16)	(NA)	WAZ, HAZ, or WHZ less than −2	(1–12)	India
Garcia-Prats et al. (2015) [89]	Ofloxacin	PO	85	Underweight (14)	(71)	WAZ less than −2	3.4 (IQR 1.9–5.2)	South Africa
Mukherjee et al. (2015) [90]	Isoniazid, rifampicin, pyrazinamide, and ethambutol	PO	127	Severely malnourished (32)	(32)	<5 years of age: weight for height <70%; > 5 years of age: BMI for age <5th percentile	(0.5–15)	India
	Isoniazid, rifampicin, pyrazinamide, and ethambutol	PO		Severely malnourished (26)	(37)			
te Brake et al. (2015) [80]	Rifampicin	PO	36	Severely malnourished (7); malnourished (4)	(25)	Severely malnourished: BMI < 16.0 kg/m^2; malnourished: BMI < 18.5 kg/m^2	35 (18–55)	Indonesia
Thee et al. (2015) [87]	Moxifloxacin	PO	23	Underweight for age (3)	(20)	WAZ less than − 2	Median 11.1 (7–15)	South Africa
Antwi et al. (2017) [55]	Isoniazid, rifampicin, pyrazinamide, and ethambutol	PO	113	HIV co-infected patients (59), median WAZ − 2.7, median HAZ − 2.8	HIV uninfected patients (54), median WAZ − 2.1, median HAZ − 1.6	WAZ, HAZ, BAZ, MUAC and head circumference scores	Median 5.0 (IQR 2.2–8.3)	Ghana
Ramachandran et al. (2016) [83]	Isoniazid, rifampicin, and pyrazinamide	PO	161	NA	(NA)	NA[e]	(1–5)	India
Rogers et al. (2016) [79]	Isoniazid	PO	30	Underweight (7); stunted (4); wasted (9)	(NA)	WAZ, HAZ, or WHZ less than − 2	(0–10)	South Africa
Ramachandran et al. (2017) [84]	Isoniazid, rifampicin, and pyrazinamide	PO	1912	Patients (961)	(951)	Body weight < 48	Median 38 (IQR 27–50)	India
Dayal et al. (2018) [86]	Isoniazid and pyrazinamide	PO	37	Severely wasted (11); underweight (19); stunted (15); severely malnourished (14)	(NA)	According to WHO growth standards	(1–15)	India
Justine et al. (2020) [76]	Isoniazid, rifampicin, pyrazinamide, and ethambutol	PO	51	Malnourished (39)	(12)	WAZ, HAZ, or BAZ less than − 2	(0.75–14)	Tanzania

Table 1 (continued)

Author (year) [Ref]	Drug	Route of administration	Total no. of patients	Malnourished patients (*n*)	Control group (*n*)[a]	Classification malnutrition	Age, years[b]	Country
Kumar et al. (2018) [91]	Levofloxacin, pyrazinamide, ethionamide, cyclosporine	PO	25	Underweight (10); stunted (14)	Not underweight (11); not stunted (7)	WAZ or HAZ less than − 2	16 (5–18)	India

AI anthropometric index, *BAZ* BMI-for-age *Z*-score, *BMI* body mass index, *HAZ* height-for-age *Z*-score, *IM* intramuscularly, *IQR* interquartile range, *IV* intravenously, *MUAC* mid-upper arm circumference, *NA* not available, *PEM* protein-energy malnutrition, *PO* orally, *SD* standard deviation, *TB* tuberculosis, *WAZ* weight-for-age *Z*-score, *WHO* World Health Organization, *WHZ* weight-for-height *Z*-score

[a]Well-nourished patients, unless stated otherwise

[b]Mean ± SD (range), unless stated otherwise

[c]Streptomycin results reported by Bolme et al. (1988)

[d]Original publication not traceable

[e] HAZ, WAZ and WHZ scores were tested as factors influencing drug concentration

for example, by the National Center for Health Statistics (NCHS)/WHO Growth Standards [35–38]. A *Z*-score of less than or equal to − 2 and greater than − 3 was considered as moderate malnutrition, while a score of less than or equal to −3 was considered as severe malnutrition. In children, the weight-for-age *Z*-score (WAZ), height-for-age *Z*-score (HAZ), and weight-for-height *Z*-score (WHZ) were used to define the degree of underweight, stunting, or wasting, respectively. In children over 5 years of age, adolescents, and adults, the HAZ, body mass index (BMI)-for-age *Z*-score (BAZ), and BMI were generally used as a nutritional status metric [37]. Severe malnutrition in children was further categorized as marasmus (absence of oedema) or kwashiorkor (presence of oedema) [39]. Other metrics used for classification in children were (1) the Wellcome Classification [40], based on the percentage of expected weight for age (WFA): > 80% WFA was graded as normal, 60–80% WFA was graded as undernutrition, < 60% WFA was graded as marasmus, and low WFA in combination with oedema and low serum protein was graded as kwashiorkor; (2) The Indian Academy of Pediatrics classification of PEM based on Khadilkar's growth charts [41]: measurements included height, weight, head circumference, and penile length (≤ 3 years of age); weight, height, BMI, penile length, and standard metabolic rate (4–8 years of age); weight, BMI, and standard metabolic rate (9–18 years of age); or (3) the left mid-upper arm circumference (MUAC) [42]. For adults, the anthropometric index (AI) [43] was used, defined as (weight[kg]/height[cm]^2) × 100, where an AI < 0.18 was considered as malnutrition.

3.4 Effect of Malnutrition on Pharmacokinetics

A complete overview of the effects of malnutrition on the various pharmacokinetic processes is presented in Tables 5, 6, 7 and 8. If possible, the effects were related to the type and severity of malnutrition or specific drug characteristics in the subsections below. The main findings with mechanistic explanations are summarized in Fig. 2.

3.4.1 Absorption

Drug absorption might be impaired because of loss of mucosal surface area and inflammation of the gastrointestinal tract, often observed in patients with severe wasting and diarrhoea (Fig. 2) [20, 44, 45]. Whereas a change in absorption rate might not be clinically relevant, an altered extent of absorption (bioavailability) might impact drug exposure and, consequently, drug effect. According to the studies included in this review, apparent bioavailability of lumefantrine, sulfadoxine, pyrimethamine, lopinavir, and efavirenz was decreased in severely malnourished patients [46–48]. On the other hand, apparent bioavailability of

Table 2 Overview of the included studies in HIV patients

Author (year) [Ref]	Drug	Route of administration	Total no. of patients	Malnourished patients (*n*)	Control group (*n*)[a]	Classification malnutrition	Age, years[b]	Country
Gatti et al. (1999) [60]	Rifabutin	PO	20	Wasting syndrome (10)	(10)	Weight loss > 10% in the last year	Wasting syndrome: 35.3 ± 6.0; controls: 37 ± 7	Italy
Brantley et al. (2003) [44]	Stavudine, zidovudine, didanosine, and/or lamivudine	PO	19	Wasting and diarrhoea (12)	(7)	Weight loss > 10% in the last 2 months	32.8 (21–54)	Brazil
Trout et al. (2004) [49]	Saquinavir	PO	100	AIDS symptomatic patients with severe body weight loss and/or diarrhoea (33)	Asymptomatic patients (30); AIDS symptomatic patients (37)	Weight loss > 10% in the last month	40 ± 10	France
Ellis et al. (2007) [50]	Nevirapine	PO	127	Stunting and wasting (NA)	(NA)	Stunting based on height-for-age, wasting based on BMI-for-age	(0.67–18)	Malawi and Zambia
Pollock et al. (2009) [92]	Nevirapine	PO	37	Mild to moderate malnutrition (12)	(25)	Weight-for-height 75–85% of the median	4.4 (0.7–16.0)	Malawi
Swaminathan et al. (2011) [17]	Nevirapine	PO	88	Underweight (51), stunted (55)	Not underweight (37), not stunted (33)	Underweight: WAZ less than − 2; stunting: HAZ less than − 2	6.5 (0.5–12)	India
Bartelink et al. (2014) [81]	Lopinavir and ritonavir	PO	116	Underweight (42)	(160)	BMI < 18.5[c]	30.5 (18–49)	Uganda
	Efavirenz	PO	105					
Fillekes et al. (2014) [68]	Zidovudine	PO	45	Moderate wasting (NA) and stunting (NA)	(NA)	NA[d]	3.4 (IQR 2.6–6.2)	Uganda
Vreeman et al. (2014) [53]	Nevirapine	PO	21	Malnourished (NA)	(NA)	NA[e]	5.4 (3–13)	Kenya
Bartelink et al. (2015) [48]	Efavirenz	PO	163	Ugandan children (32) [44% malnourished]	Dutch children (52) [10% underweight]	WAZ, HAZ, or BAZ less than − 2	(0.7–7)	Uganda
	Lopinavir	PO		Ugandan children (83) [47% malnourished]	French children (56) [14% underweight]			
	Nevirapine	PO		Ugandan children (48) [50% malnourished]	American children (96) [14% malnourished]			

Table 2 (continued)

Author (year) [Ref]	Drug	Route of administration	Total no. of patients	Malnourished patients (*n*)	Control group (*n*)[a]	Classification malnutrition	Age, years[b]	Country
Archary et al. (2018) [33]	Lopinavir	PO	63	Severe acute malnutrition (34)	Patients after nutritional recovery (29) [WHZ greater than or equal to −2, >15% weight gain, or resolution of oedema and return of appetite]	WHZ less than −3, MUAC < 115 mm, or peripheral oedema	0.9 (0.1–3.9)	South Africa
Archary et al. (2019) [34]	Abacavir and lamivudine	PO	75	Severe acute malnutrition (36)	Patients after nutritional recovery (39) [WHZ greater than or equal to − 2, > 15% weight gain, or resolution of oedema and return of appetite]	WHZ less than − 3, MUAC < 115 mm, or peripheral oedema	(0.08–12)	South Africa

BAZ BMI-for-age *Z*-score, *BMI* body mass index, *GWG* gestational weight gain, *HAZ* height-for-age *Z*-score, *HFIAS* household food insecurity access scale, *HHS* household hunger scale, *MUAC* mid-upper arm circumference, *NA* not available, *PO* orally, *SD* standard deviation, *TBW%* total body water percentage, *WAZ* weight-for-age *Z*-score, *WHZ* weight-for-height *Z*-score

[a]Well-nourished patients, unless stated otherwise

[b]Mean ± SD (range), unless stated otherwise

[c]BMI, GWG, MUAC, HFIAS and HHS scores were tested as factors influencing drug concentration

[d]Weight-for-age and height-for-age scores were tested as factors influencing drug concentration

[e]MUAC, WAZ scores and TBW% were tested as factors influencing pharmacokinetic parameters

Table 3 Overview of the included studies in malaria patients

Author (year) [Ref]	Drug	Route of administration	Total no. of patients	Malnourished patients (*n*)	Control group (*n*)[a]	Classification malnutrition	Age, years[b]	Country
Wharton et al. (1970) [69]	Chloroquine	PO	13	Kwashiorkor uninfected children (10)	Well-nourished uninfected children (3); Kwashiorkor children after 2–3 weeks recovery (7)	NA	Children	Uganda
Tulpule and Krishnaswamy (1983) [74]	Chloroquine	PO	15	Undernourished uninfected subjects (8)	Well-nourished uninfected subjects (7)	AI <0.18	(25–40)	India
Walker et al. (1987) [70]	Chloroquine	PO	11	Kwashiorkor uninfected subjects (5)	Well-nourished uninfected subjects (6)	Wellcome classification	2.5 (2–3.5)	Nigeria
Salako et al. (1989) [72]	Quinine	PO	13	Kwashiorkor uninfected subjects (6)	Well-nourished uninfected subjects (7)	Universally accepted clinical grounds	2.2 ± 0.6 (1.5–3)	Nigeria
Treluyer et al. (1996) [26]	Quinine	IM	15	Undernourished patients (8)	Well-nourished patients (7)	MUAC/head circumference ratio < 0.28	(0.75–5)	Gabon
Pussard et al. (1999) [58]	Quinine	IV	40	Malnourished uninfected subjects (10); malnourished patients (10)	Well-nourished uninfected subjects (10)	At least 2/3 measures (WAZ, HAZ and WHZ) less than − 2	(2–6)	Niger
Dua et al. (2002) [71]	Chloroquine	PO	22	Malnourished tribal uninfected volunteers (6)	Healthy volunteers [AI > 0.2] (5)	AI < 0.18	Mean 29–34	India
				Malnourished tribal patients (6)	Nontribal patients [AI > 0.2] (5)			
WWARN (2015) [93]	Artemether-lumefantrine	PO	567	Underweight patients < 3 years of age (28)	Well-nourished patients < 3 years of age (262)	WAZ less than − 2	3 (1–4)	Africa and Asia
				Underweight patients 3–4 years of age (48)	Well-nourished patients 3–4 years of age (229)			
Kadam et al. (2016) [52]	Chloroquine	PO	25	PEM (13)	(12)	IAP classification	(5–12)	India
de Kock et al. (2018) [46]	Sulfadoxine and pyrimethamine	PO	383	Malnourished (41)	(326)	− 3 ≤ WAZ < − 2	(0.25–4.9)	Africa
				Severely malnourished (16)		WAZ less than − 3		
Chotsiri et al. (2019) [47]	Artemether-lumefantrine	PO	263	SAM (131)	Non-SAM (160)	WHZ less than −3 or MUAC < 115 cm	(0.5–4.9)	Mali and Niger

AI anthropometric index, *IAP* Indian Academy of Pediatrics, *IM* intramuscularly, *IV* intravenously, *MUAC* mid-upper arm circumference, *HAZ* height-for-age *Z*-score, *NA* not available, *PEM* protein-energy malnutrition, *PO* orally, *SAM* severe acute malnutrition, *SD* standard deviation, *WAZ* weight-for-age *Z*-score, *WHZ* weight-for-height *Z*-score

[a]Well-nourished patients, unless stated otherwise

[b]Mean ± SD (range), unless stated otherwise

abacavir was increased in severe acute malnutrition [34], and increased exposure for saquinavir [49], nevirapine [50], and ivermectin [51] in severely wasted [49, 50]/malnourished [51] patients was potentially caused by increased absorption. As suggested by the literature, the increased absorption of these drugs is likely due to decreased P-glycoprotein activity in the enterocytes or the enlargement of their tight junctions, enhancing paracellular passive uptake of the drug [21, 49].

Table 4 Overview of the included studies in NTD patients

Author (year) [Ref]	Disease	Drug	Route of administration	Total no. of patients	Malnourished patients (*n*)	Control group (n)	Classification malnutrition	Age, years[a]	Country
Schulz et al. (2019) [51]	Helminthiasis	Ivermectin	PO	80	(NA)	Well-nourished patients (NA)	NA[b] [total BMI: mean 15 (range 12–24)]	(2–5)	Ivory Coast
	Helminthiasis	Ivermectin	PO	120	(NA)	Well-nourished patients (NA)	NA[b] [total BMI: mean 16 (range 12–25)]	(6–12)	Ivory Coast
Palić et al. (2020) [94]	Visceral leishmaniasis	Miltefosine	PO	51	(NA)	Well-nourished patients (NA)	BAZ, WHZ or HAZ less than −2	(4–12)	Kenya, Sudan, Uganda

BAZ BMI-for-age *Z*-score, *BMI* body mass index, *HAZ* height-for-age *Z*-score, *NA* not available, *NTD* neglected tropical diseases, *PO* orally, *WHZ* weight-for-height *Z*-score

[a]Range

[b]The correlation between BMI and pharmacokinetic parameters was investigated

3.4.2 Distribution and Protein Binding

Severe malnutrition is associated with changes in body composition, such as increased extracellular body water and decreased lean body mass, and the presence of oedema in kwashiorkor, leading to decreased drug distribution of lipophilic drugs and increased distribution of hydrophilic drugs (Fig. 2) [19, 20]. This was demonstrated by various identified studies: volume of distribution was decreased for the lipophilic drug isoniazid in kwashiorkor [31], and for chloroquine [52] and nevirapine [48, 53] in malnutrition. Volume of distribution was increased for the hydrophilic drug streptomycin in kwashiorkor [54]. These effects seem to exhibit mainly in kwashiorkor, as the effects could not be demonstrated for isoniazid and streptomycin in moderate malnutrition [19, 52, 55].

Nonetheless, distribution of highly protein-bound drugs with a high extraction ratio may be changed because of altered plasma protein levels (Fig. 2) [19, 20, 56]. Basic drugs mainly bind to albumin, whereas acidic drugs mainly bind to α1-acid glycoprotein. Binding of drugs to α1-acid glycoprotein becomes pharmacologically relevant when the dissociation constant for α1-acid glycoprotein is <0.1 times lower compared with albumin [25]. Malnutrition in combination with infectious inflammation is associated with low serum albumin levels [23] but with increased inflammatory proteins such as α1-acid glycoprotein [57, 58]. This was supported by some of the studies: protein binding for rifampicin was decreased [59] and volume of distribution for lopinavir and efavirenz was increased in malnourished patients [48], potentially causing increased drug elimination and resulting decreased drug exposure. The increased levels of α1-acid glycoprotein in malnutrition resulted in higher quinine plasma protein binding and increased exposure in malnourished patients [58]. For the weak bases rifabutin [60] and saquinavir [49], the decreased volume of distribution and resulting increased C_{max} in wasting [49, 60] might also be the result of elevated α1-acid glycoprotein binding [61]. However, it should be noted that the increased levels of α1-acid glycoprotein in malnourished patients are a result of infections, often accompanied by malnutrition. The effect of malnutrition itself on α1-acid glycoprotein levels has not been well-investigated. Although it is believed that the humoral immune response is well preserved in malnourished patients during infection, some studies demonstrated an impaired acute-phase protein response in children with severe PEM, especially in kwashiorkor [62]. This complicates the evaluation of α1-acid glycoprotein binding in relation to malnutrition.

3.4.3 Metabolism and Excretion

Metabolism of hepatically cleared drugs may be altered in severe malnutrition due to impaired hepatic functioning by fat infiltration of the liver and decreased synthesis and activity of certain phase I and II metabolizing enzymes [19, 20, 45, 63, 64]. Impaired GFR in severe malnutrition may impact the excretion of renally cleared drugs (Fig. 2) [19, 20]. Decreased elimination was observed for the hepatically cleared drug isoniazid in kwashiorkor or different degrees of malnutrition [18, 31, 65–67], for saquinavir and zidovudine in wasting [49, 68], for chloroquine in kwashiorkor [69, 70] and malnutrition [52, 71], and for quinine in kwashiorkor [72] and severely malnourished patients

Table 5 Pharmacokinetic results of TB studies

Drug	Absorption	Exposure	Distribution	Elimination	PK methodology	References
Isoniazid			V_d/F decreased	CL/F decreased*; $T_{½}$ increased*	NCA	Buchanan et al. (1979) [31]
		AUC and C_{max} unchanged		$T_{½}$ increased	NCA	Eriksson et al. (1988) [67]
		AUC_{∞} unchanged		$T_{½}$ increased	NCA	Garg et al. (1988) [65]
	T_{max} unchanged	AUC and C_{max} increased		$T_{½}$ increased; k_e decreased	NA	Seth et al. (1992) [18]
		C_{2h} unchanged		$T_{½}$ and k_e unchanged	NCA	Seifart et al. (1995) [32]
		C_{max} unchanged			NCA	McIlleron et al. (2009) [82]
	T_{max} unchanged	AUC_{24} and AUC increased; C_{max} unchanged	V_d/F unchanged	CL/F decreased; $T½$ and k_e unchanged	CA	Roy et al. (2010) [66]
		AUC_{24} unchanged			NCA	Verhagen et al. (2012) [78]
		AUC_8 and C_{max} decreased in stunting*			NCA	Ramachandran et al. (2013) [77]
	T_{max} unchanged	AUC_4, C_{2h}, and C_{max} unchanged			NCA	Mukherjee et al. (2015) [90]
	T_{max} decreased*	AUC_8 and C_{max} unchanged	Normalized V_d/F unchanged	Normalized CL/F unchanged	NCA	Antwi et al. (2017) [55]
		AUC_8 decreased with low WAZ; C_{max} decreased with low HAZ			NCA	Ramachandran et al. (2016) [83]
			V_{max} and K_m unchanged	k_e unchanged	CA	Rogers et al. (2016) [79]
		C_{2h} decreased*			NCA	Ramachandran et al. (2017) [84]
		AUC_8 and C_{max} unchanged			NCA	Dayal et al. (2018) [86]
		C_{2h} decreased*			NCA	Justine et al. (2020) [76]
Rifampicin		AUC_{∞} and C_{max} decreased*	Plasma protein binding decreased*	CL/F and CL_R increased*; $T_{½}$ unchanged	NCA	Polasa et al. (1984) [59]
		AUC_{∞} increased		$T_{½}$ unchanged	NCA	Garg et al. (1988) [65]
	T_{max} unchanged	AUC and C_{max} increased		$T_{½}$ and k_e unchanged	NA	Seth et al. (1992) [18]
		AUC_{24} unchanged			NCA	Verhagen et al. (2012) [78]
		AUC_8 and C_{max} decreased in stunting* and underweight*			NCA	Ramachandran et al. (2013) [77]
	T_{max} unchanged	AUC_4, C_{2h}, and C_{max} unchanged			NCA	Mukherjee et al. (2015) [90]
	T_{max} unchanged	AUC_{24} and C_{max} unchanged	V_d/F and f_{free} unchanged	CL/F and $T_{½}$ unchanged	NCA	te Brake et al. (2015) [80]
	T_{max} unchanged	AUC_8 and C_{max} decreased*	Normalized V_d/F unchanged	Normalized CL/F increased*	NCA	Antwi et al. (2017) [55]
		AUC_8 and C_{max} unchanged			NCA	Ramachandran et al. (2016) [83]

Table 5 (continued)

Drug	Absorption	Exposure	Distribution	Elimination	PK methodology	References
		C_{2h} unchanged			NCA	Ramachandran et al. (2017) [84]
		C_{2h} decreased*			NCA	Justine et al. (2020) [76]
Pyrazinamide	T_{max} unchanged	AUC_{24} and C_{max} decreased; AUC_{24}/dose and C_{max}/dose unchanged			NCA	Graham et al. (2006) [88]
		AUC_{24} decreased			NCA	Verhagen et al. (2012) [78]
		AUC_8 and C_{max} decreased in stunting* and underweight*			NCA	Ramachandran et al. (2013) [77]
	T_{max} unchanged	AUC_4, C_{2h}, and C_{max} unchanged			NCA	Mukherjee et al. (2015) [90]
	T_{max} decreased*	AUC_8 decreased*; C_{max} unchanged	Normalized V_d/F unchanged	Normalized CL/F increased*	NCA	Antwi et al. (2017) [55]
		AUC_8 and C_{max} unchanged			NCA	Ramachandran et al. (2016) [83]
		C_{2h} decreased*			NCA	Ramachandran et al. (2017) [84]
		AUC_8 decreased in severe wasting*, stunting*, and severe malnutrition*; C_{max} decreased in severe malnutrition*			NCA	Dayal et al. (2018) [86]
		C_{2h} unchanged			NCA	Justine et al. (2020) [76]
		AUC_8 unchanged; C_{max} decreased in underweight*			NCA	Kumar et al. (2018) [91]
Ethambutol	T_{max} decreased	AUC_{24} and AUC_{24}/dose unchanged; C_{max} and C_{max}/dose increased			NCA	Graham et al. (2006) [88]
	T_{max} unchanged	AUC_4, C_{2h}, and C_{max} unchanged			NCA	Mukherjee et al. (2015) [90]
	T_{max} unchanged	AUC_8 and C_{max} decreased*	Normalized V_d/F increased*	Normalized CL/F increased*	NCA	Antwi et al. (2017) [55]
		C_{2h} unchanged			NCA	Justine et al. (2020) [76]
Streptomycin	$T_{½,abs}$ unchanged		V_d/F increased in kwashiorkor*	CL/F unchanged; $T_{½,el}$ increased in kwashiorkor*	CA	Bolme et al., (1988) [54]
	T_{max} increased	Concentrations unchanged	V_d/F and plasma protein binding unchanged	$T½$ unchanged	NCA	Prasad and Krishnaswamy (1978) [75]
Ofloxacin	T_{max} unchanged	AUC_8, AUC_{24}, and C_{max} unchanged	V_d/F unchanged	CL/F and $T_{½}$ unchanged	NCA	Garcia-Prats et al. (2015) [89]
Moxifloxacin	T_{max} unchanged	AUC_8 decreased*; C_{max} unchanged			NCA	Thee et al. (2015) [87]
Levofloxacin		AUC_8 and C_{max} unchanged			NCA	Kumar et al. (2018) [91]

Table 5 (continued)

Drug	Absorption	Exposure	Distribution	Elimination	PK methodology	References
Ethionamide		AUC_8 and C_{max} unchanged			NCA	Kumar et al. (2018) [91]
Cyclosporine		AUC_8 and C_{max} unchanged			NCA	Kumar et al. (2018) [91]

AUC area under the curve, AUC_4 AUC from time zero to 4 h, AUC_8 AUC from time zero to 8 h, AUC_{24} AUC from time zero to 24 h, AUC_∞ AUC from time zero to infinity, C_{2h} concentration at 2 h, *CA* compartmental analysis, *CL/F* apparent oral clearance, CL_R renal clearance, C_{max} peak concentration, f_{free} unbound fraction, *HAZ* height-for-age *Z*-score, k_a absorption rate constant, k_e elimination rate constant, K_m drug concentration where enzyme achieves half V_{max}, *NA* not available, *NCA* noncompartmental analysis, *PK* pharmacokinetic, $T_{½,abs}$ absorption half-life, $T_{½,el}$ elimination half-life, $T_{½}$ terminal half-life, *TB* tuberculosis, T_{max} time to maximum plasma concentration, V_d/F apparent volume of distribution, V_{max} maximum enzyme binding rate, *WAZ* weight-for-age *Z*-score

*Significant difference

[58]. An increased AUC and slower clearance of isoniazid in malnutrition is likely caused by reduced metabolism by acetylation, although the effect of malnutrition on the process of acetylation could not be clearly determined [73]. Saquinavir, zidovudine, chloroquine, and quinine metabolism is mainly driven by cytochrome P450 enzymes, whose activity is reduced in malnutrition [64]. Another reason for the decreased metabolism of, for example, quinine and saquinavir could be the increase of α1-acid glycoprotein levels in kwashiorkor and severe malnutrition, leading to a decrease in the unbound fraction and, consequently, lower hepatic uptake [26, 58]. Likewise, the increased excretion of chloroquine [74], quinine [26], ethambutol [55], rifampicin [55, 59], lopinavir [48], and efavirenz [48] in (moderate) malnutrition might be caused by the increased free fraction of these highly albumin-bound drugs. For the renally cleared drug streptomycin, excretion was decreased in kwashiorkor [54], but unchanged in malnutrition [75].

3.5 Type of Malnutrition

The alterations in drug exposure likely depend on the patient population, as for some drugs relationships could be identified between the type or severity of malnutrition and the effect on drug exposure in these studies. For example, isoniazid and rifampicin exposure was decreased in moderately malnourished patients [59, 76, 77], potentially due to either reduced absorption or decreased protein binding and, consequently, an increased volume of distribution or elevated drug clearance [59]. On the other hand, isoniazid and rifampicin exposure was increased in severe malnutrition [18, 65, 66], potentially caused by a more pronounced suppression of enzyme activity in severe malnutrition [65]. On the other hand, chloroquine exposure was decreased in kwashiorkor, potentially caused by decreased bioavailability [70]. Nevirapine concentrations were decreased in stunted children but increased in wasted children [50]. This might be explained by the different pathophysiological conditions: the decreased absorption and enhanced clearance of protein-bound drugs associated with stunting might lead to decreased serum concentrations, whereas reduced metabolism in wasting might cause an increase in plasma concentration [17].

3.6 Study Design and Data Analysis

The effects of malnutrition on PRD drug pharmacokinetics were not always replicable, which might be due to the underpowered study designs. The sample size was small (< 50 participants) in the majority of studies, which can be the reason why a potentially expected effect could not be demonstrated in some of the studies [32, 67, 78–81]. The effect might not be traceable because of the small difference in malnutrition status between patient groups [32, 55, 76, 78, 79, 81]. In other studies, the number of malnourished patients was unknown [82, 83] or malnutrition was poorly diagnosed [84].

The studies included in this review include a heterogeneous patient population with a wide variety in the source and severity of malnutrition, as well as different metrics used to define and score malnourished patients. In order to identify the effects of malnutrition on pharmacokinetics, a standard and generic definition of the different types of malnutrition is needed to compare different studies. Moreover, the studied populations included patients of different age ranges and patients infected by different PRDs, different severity of disease, as well as non-infected subjects. Disease activity with increased inflammatory cytokine levels, local disease activity in the gastrointestinal tract, and comedications can all impact pharmacokinetics. Malnutrition may impact physiological processes differently in patients of different ages. All these sources of heterogeneity complicate the extraction of the effects of malnutrition on pharmacokinetics. Moreover, the dosing guidelines might impact drug exposure in the different populations. When fixed dosing is applied, the dose per kilogram of body weight will be higher in malnourished patients after

Table 6 Pharmacokinetic results of HIV studies

Drug	Absorption	Exposure	Distribution	Elimination	PK methodology	References
Rifabutin	T_{max} decreased	AUC unchanged; C_{max} increased*; C_{24h} increased*	V_d/F decreased; V_d/F/kg decreased	CL/F unchanged; CL/F/kg unchanged; $T_{½}$ decreased	NCA	Gatti et al. (1999) [60]
Stavudine		C_{max} decreased*			NCA	Brantley et al. (2003) [44]
Didanosine		C_{max} decreased			NCA	Brantley et al. (2003) [44]
Lamivudine		C_{max} unchanged			NCA	Brantley et al. (2003) [44]
	k_a unchanged		V_d/F unchanged	CL/F unchanged	CA	Archary et al. (2019) [34]
Abacavir	k_a unchanged, F increased*		V_c/F unchanged; Q/F unchanged; V_p/F unchanged	CL/F unchanged	CA	Archary et al. (2019) [34]
Saquinavir	T_{lag} decreased*; k_a decreased*; T_{max} unchanged	AUC increased*; C_{max} increased*	V_d/F decreased*	CL/F decreased*; k_e decreased*	CA	Trout et al. (2004) [49]
Nevirapine		C_{max} increased in wasting*; C_{max} decreased in stunting*			NCA	Ellis et al. (2007) [50]
		AUC_{12}, C_{max}, and C_{trough} unchanged			NCA	Pollock et al. (2009) [92]
		C_{2h} decreased in stunting*; C_{trough} unchanged			NCA	Swaminathan et al. (2011) [17]
	k_a unchanged		V_d/F decreased with increasing TBW%	CL/F unchanged	CA	Vreeman et al. (2014) [53]
	F increased*		V_d/F decreased*	CL/F decreased*	CA	Bartelink et al. (2015) [48]
Lopinavir	F unchanged			CL/F unchanged	CA	Bartelink et al. (2014) [81]
	F decreased*		V_d/F increased*	CL/F increased*	CA	Bartelink et al. (2015) [48]
	k_a unchanged	C_{max} decreased	V_d/F unchanged	CL/F unchanged	CA	Archary et al. (2018) [33]
Efavirenz	F unchanged			CL/F unchanged	CA	Bartelink et al. (2014) [81]
	F decreased*		V_d/F increased*	CL/F increased*	CA	Bartelink et al. (2015) [48]
Ritonavir	F unchanged			CL/F unchanged	CA	Bartelink et al. (2014) [81]
Zidovudine		C_{max} unchanged			NCA	Brantley et al. (2003) [44]
		AUC_{12} increased in wasting*, C_{max} and C_{12h} unchanged		CL/F decreased in wasting*, $T_{½}$ unchanged	NCA	Fillekes et al. (2014) [68]

AUC area under the curve, AUC_{12} area under the curve from time zero to 12 h, C_{2h} concentration at 2 h, C_{12h} concentration at 12 h, C_{24h} concentration at 24 h; *CA* compartmental analysis, *CL/F* apparent oral clearance, C_{max} peak concentration, C_{trough} trough concentration, F apparent bioavailability, k_a absorption rate constant, k_e elimination rate constant, *NCA* noncompartmental analysis, *PK* pharmacokinetic, Q/F apparent intercompartmental clearance, $T_{½}$ terminal half-life, *TBW%* total body water percentage, T_{lag} absorption lag time, T_{max} time to reach C_{max}, V_c/F central volume of distribution, V_d/F volume of distribution, V_p/F peripheral volume of distribution

*Significant difference

Table 7 Pharmacokinetic results of malaria studies

Drug	Absorption	Exposure	Distribution	Metabolism	Elimination	PK methodology	References
Chloroquine				Drug/metabolite ratio increased*		NCA	Wharton and McChesney (1970) [69]
		AUC unchanged			CL/*F* increased*; $T_{½}$ unchanged	NCA	Tulpule and Krishnaswamy (1983) [74]
		AUC decreased*		Drug/metabolite ratio increased	$T_{½}$ unchanged	NCA	Walker et al. (1987) [70]
	T_{max} increased	AUC_{168}, AUC_{∞}, and C_{max} unchanged		Drug/metabolite ratio increased	CL/*F* unchanged; $T_{½}$ unchanged	NCA	Dua et al. (2002) [71]
		AUC_{∞} increased; C_{max} unchanged	V_d/F decreased	Drug/metabolite ratio unchanged	CL/*F* decreased; $T_{½}$ unchanged	NCA	Kadam et al. (2016) [52]
Quinine	$T_{½,abs}$ increased*	AUC increased*; C_{max} decreased*			CL/*F* decreased*; $T_{½}$ increased*	CA	Salako et al. (1989) [72]
	T_{max} decreased*	C_{max} unchanged; C_{12h} decreased	V_d/F and plasma protein binding unchanged	Drug/metabolite ratio decreased*	CL/*F* increased*; $T_{½}$ decreased*	NCA	Treluyer et al. (1996) [26]
		AUC_8 and C_{max} increased*	V_d/F decreased*; plasma protein binding increased*; erythrocyte binding unchanged		CL/*F* decreased*; $T_{½}$ increased*	CA	Pussard et al. (1999) [58]
Lumefantrine		C[a] decreased in children < 3 years of age				NCA	WWARN (2015) [93]
	F decreased*					CA	Chotsiri et al. (2019) [47]
Sulfadoxine	*F* decreased*					CA	de Kock et al. (2018) [46]
Pyrimethamine	*F* decreased*					CA	de Kock et al. (2018) [46]

AUC area under the curve, AUC_8 AUC from time zero to 8 h, AUC_{168} AUC from time zero to 168 h, AUC_{∞} AUC from time zero to infinity, C_{12h} concentration at 12 h, *CA* compartmental analysis, *CL/F* apparent oral clearance, C_{max} peak concentration, *F* apparent bioavailability, *NCA* non-compartmental analysis, *PK* pharmacokinetic, $T_{½,abs}$ apparent absorption half-life, $T_{½}$ terminal half-life, T_{max} time to reach C_{max}, V_d/F volume of distribution

*Significant difference

[a]Day 7 concentrations at different time points

fixed dosing, but even when using a linear weight-based dosing, exposure differences might be expected.

3.7 Conclusions and Recommendations

Forty-nine studies were included in this review, with most of the studies conducted in TB, HIV, and malaria patients. For most of the NTDs, no studies were identified at all. In 21/29 of the PRD drugs included in this review, pharmacokinetics

Table 8 Pharmacokinetic results of NTD studies

Drug	Absorption	Exposure	Distribution	Excretion	PK methodology	References
Ivermectin		AUC increased*			NCA	Schulz et al. (2019) [51]
Miltefosine	F and k_a unchanged		V_c/F, Q/F, and V_p/F unchanged	CL/F unchanged	CA	Palić et al. (2020) [94]

AUC area under the curve, *CA* compartmental analysis, *CL/F* apparent oral clearance, *F* apparent bioavailability, k_a absorption rate constant, *NCA* noncompartmental analysis, *NTD* neglected tropical diseases, *PK* pharmacokinetic, *Q/F* apparent intercompartmental clearance, V_c/F apparent central volume of distribution, V_p/F apparent peripheral volume of distribution

*Significant difference

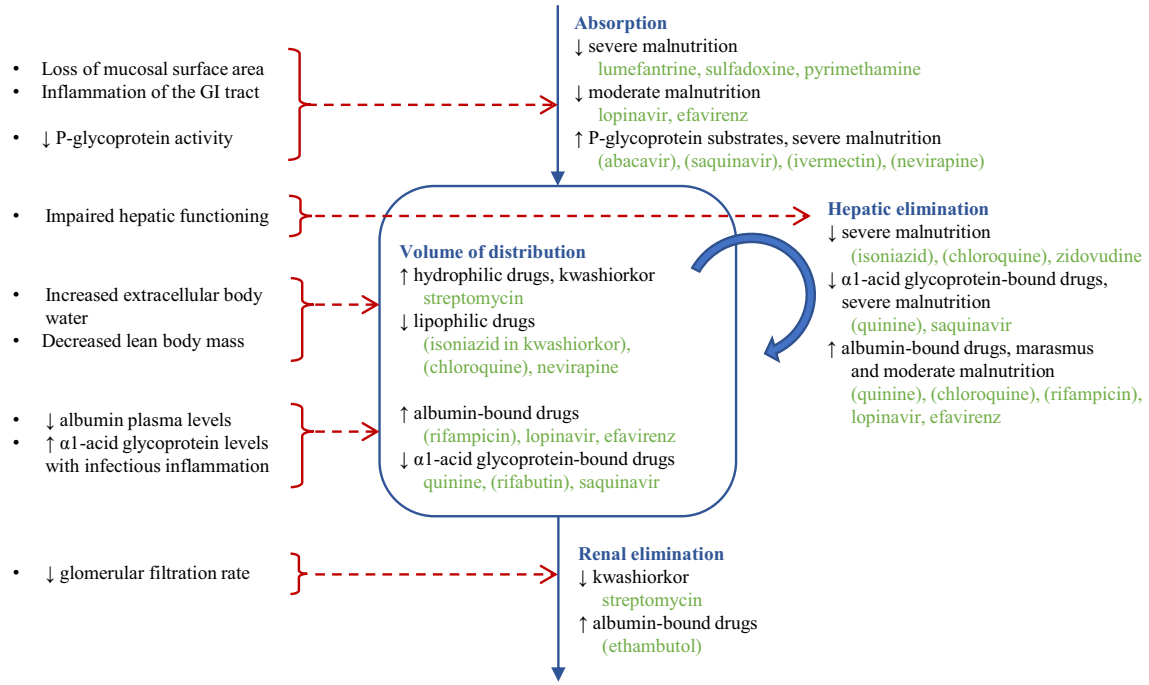

Fig. 2 Alterations in drug pharmacokinetics by malnutrition. Figure summarizes the main pathophysiological changes (left) and the associated effects on drug pharmacokinetics in different pharmacokinetic stages, illustrated by the effects found for drugs against poverty-related infectious diseases (right). Drug names are mentioned when the evidence for the effect was considered strong, or mentioned in brackets when the evidence for the effect was considered weak

were affected by malnutrition. A complete overview of the literature is summarized in Tables 1, 2, 3 4, 5, 6, 7, and 8. The included studies were relatively small and heterogeneous. However, trends were observed for specific classes of drugs and types of malnutrition. An interpretation of the results by the reviewers is summarized in Fig. 2, where the effects are categorized as strong or weak effects based on the level of evidence. The bioavailability of lumefantrine, sulfadoxine, pyrimethamine, lopinavir, and efavirenz was decreased in severely malnourished patients, but increased for the P-glycoprotein substrates abacavir, saquinavir, nevirapine, and ivermectin. Volume of distribution was decreased for the lipophilic drugs isoniazid, chloroquine, and nevirapine, and for the α1-acid glycoprotein-bound drugs quinine, rifabutin, and saquinavir. Volume of distribution was increased for the hydrophilic drug streptomycin, and for the albumin-bound drugs rifampicin, lopinavir, and efavirenz. Drug elimination was decreased in severe malnutrition for the hepatically cleared drugs isoniazid, chloroquine, quinine, zidovudine, and saquinavir, and for the renally cleared drug streptomycin. On the other hand, elimination was increased for the albumin-bound drugs quinine, chloroquine, rifampicin, lopinavir, efavirenz, and ethambutol.

The alterations in pharmacokinetics in malnourished patients might impact clinical efficacy and/or toxicity and therefore may require dose adjustments in the malnourished population. A systematic review on antibiotics suggested that normal doses of penicillins, cotrimoxazole and gentamicin are well-tolerated in malnourished children, while the dose or frequency of chloramphenicol requires adjustment,

although evidence was not sufficiently strong to establish dosing recommendations [85]. These studies suggested a clinically relevant impact of malnutrition on the pharmacokinetics of certain PRD drugs. Various studies included in this systematic review addressed the need for dose adjustments in the malnourished population for isoniazid [18, 67, 76, 77, 83, 84], rifampicin [55, 76, 77], pyrazinamide [55, 77, 84, 86], ethionamide [55], moxifloxacin [87], stavudine [44], nevirapine [17], chloramphenicol [70], and ivermectin [51]. A specifically adapted treatment regimen in malnourished patients was only suggested for nevirapine [50] and quinine [26]. Other studies concluded that the identified effect on pharmacokinetics was of no clinical relevance, and no dose adjustment might be needed for rifampicin [59, 65], rifabutin [60], chloramphenicol [52], quinine [58], and pyrimethamine [46]. These results imply a trend between the degree of malnutrition and the pharmacokinetic effect size: a clinically relevant effect was observed in severe malnutrition and kwashiorkor [18, 50, 67, 70, 86], except for quinine [58], whereas no dose adjustment was needed in mainly moderately malnourished patients. The clinical impact of these pharmacokinetic effects in severely malnourished patients is highly relevant as these patients are mostly excluded in clinical trials, whereas, in reality, these patients constitute a sizeable proportion of the PRD patient populations. This highlights the importance to include severely malnourished patients in pharmacokinetic studies for PRD drugs.

This systematic review summarizes the main effects of malnutrition on PRD drug pharmacokinetics, with potentially clinically relevant effects on treatment response. This overview can be used as a basis to predict the effects of malnutrition on PRD drug pharmacokinetics. This might be relevant for the study design of clinical studies, to account for the possible clinically relevant effects of malnutrition on pharmacokinetics, based on the drug characteristics and types of malnutrition in the studied population.

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Declarations

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Conflicts of interest Luka Verrest, Erica A. Wilthagen, Jos H. Beijnen, Alwin D.R. Huitema and Thomas P.C. Dorlo have no conflicts of interest to declare.

Author contributions LV and TPCD were responsible for the collection and summary of the study data, as well as the draft of the first version of the manuscript. EW was responsible for the systematic literature search and summary of the search in the manuscript. All authors participated in the interpretation of the study results and in the drafting, critical revision and approval of the final version of the manuscript.

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