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
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
Pharmacokinetics in Malnutrition and Poverty-Related Diseases

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 ($C_{\text{max}}$) and time to reach $C_{\text{max}}$ ($T_{\text{max}}$) were derived by visual inspection of the data, area under the curve (AUC) was calculated by the trapezoidal rule, and/or half-life ($T_{1/2}$) 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 ($C_t$), $C_{\text{max}}$, and trough concentration ($C_{\text{trough}}$); drug absorption was characterized by bioavailability; drug absorption rate was characterized by $T_{\text{max}}$, 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 ($V_{\text{max}}$). 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
| Author (year) [Ref] | Drug | Route of administration | Total no. of patients | Malnourished patients (n) | Control group (n)§ | Classification malnutrition | Age, years§ | 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 |
| Prasad and Krishnaswamy (1978) [75] | Streptomycin | IM | 34 | Underweight (6); marasmic (6); kwashiorkor (3) | AI < 0.18 | 4.9 (0.5–12) | India |
| 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 |
| 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 |
| 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 |
| Mcllerson et al. (2009) [82] | Ethambutol | 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 |
| Author (year) [Ref] | Drug | Route of administration | Total no. of patients | Malnourished patients (n) | Control group (n) | Classification malnutrition | Age, years | 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 |
| te Brake et al. (2015) [80] | Rifampicin | PO | 36 | Severely malnourished (7); malnourished (4) | (25) | Severely malnourished: BMI < 16.0 kg/m²; malnourished: BMI < 18.5 kg/m² | 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 | (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 |
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
| Author (year) [Ref] | Drug | Route of administration | Total no. of patients | Malnourished patients (n) | Control group (n)a | Classification malnutrition | Age, yearsb | Country |
|---------------------|------|-------------------------|----------------------|--------------------------|------------------|-----------------------------|------------|---------|
| Gatti et al. (1999) [60] | Rifabutin | PO | 20 | Wasting syndrome (10) | (10) | Weight loss > 10% in the last year | 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 < 18.5c | 30.5 (18–49) | Uganda |
| | Efavirenz | PO | 105 | Moderate wasting (NA) and stunting (NA) | (NA) | NAd | 3.4 (IQR 2.6–6.2) | Uganda |
| Fillekes et al. (2014) [68] | Zidovudine | PO | 45 | Moderate wasting (NA) | (NA) | NAe | 5.4 (3–13) | Kenya |
| Vreeman et al. (2014) [53] | Nevirapine | PO | 21 | Malnourished (NA) | (NA) | NAe | 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] | Uganda |
| | Nevirapine | PO | Ugandan children (48) [50% malnourished] | American children (96) [14% malnourished] | Uruguayan children (110) [60% malnourished] |
### Table 2 (continued)

| Author (year) [Ref] | Drug                        | Route of administration | Total no. of patients | Malnourished patients (n) | Control group (n)^c | 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 |

**Notes:**

- 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
- aWell-nourished patients, unless stated otherwise
- bMean ± SD (range), unless stated otherwise
- cBMI, GWG, MUAC, HFIAS and HHS scores were tested as factors influencing drug concentration
- dWeight-for-age and height-for-age scores were tested as factors influencing drug concentration
- eMUAC, WAZ scores and TBW% were tested as factors influencing pharmacokinetic parameters
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 3** Overview of the included studies in malaria patients

| Author (year) | Drug | Route of administration | Total no. of patients | Malnourished patients (n) | Control group (n) | Classification malnutrition | Age, yearsb | 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) | | | | Nigeria |
| Salako et al. (1989) [72] | Quinine | PO | 13 | Kwashiorkor uninfected subjects (6) | Well-nourished uninfected subjects (7) | | | | Nigeria |
| Trelayer 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) | | | |
| 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 |
| 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 | | | Africa and Asia |
| Kadam et al. (2016) [52] | Chloroquine | PO | 25 | PEM (13) | IAP classification | (5–12) | | | India |
| de Kock et al. (2018) [46] | Sulfadoxine and pyrimethamine | PO | 383 | Malnourished (41) | | − 3 ≤ WAZ < − 2 | (0.25–4.9) | | Africa |
| 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

Δ Adis
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 $C_{\text{max}}$ 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.

### Table 4 Overview of the included studies in NTD patients

| Author (year) | Disease | Drug | Route of administration | Total no. of patients | Malnourished patients (n) | Control group (n) | Classification of malnutrition | Age, years | Country |
|---------------|---------|------|--------------------------|-----------------------|--------------------------|-------------------|-------------------------------|------------|---------|
| Schulz et al. (2019) [51] | Helminthiasis | Ivermectin | PO | 80 | (NA) | Well-nourished patients (NA) | NA\[^a\] | (2–5) | 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 |

\[^a\]The correlation between BMI and pharmacokinetic parameters was investigated

\[^b\]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

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; $T_{1/2}$ increased* | NCA            | Buchanan et al. (1979) [31] |
|            |            |          | $T_{max}$ unchanged| $T_{max}$ increased           | NCA            | Eriksson et al. (1988) [67] |
|            |            |          | $AUC_{24}$ increased| $T_{max}$ increased         | NCA            | Garg et al. (1988) [65]   |
|            |            |          | $C_{2h}$ unchanged  | $T_{max}$ increased; $k_c$ decreased | NA             | Seth et al. (1992) [18]   |
|            |            |          | $C_{max}$ unchanged | $T_{max}$ and $k_c$ unchanged | NCA            | Seifart et al. (1995) [32] |
|            |            |          | $AUC_{24}$ and $AUC$ increased; $C_{max}$ unchanged | $V_d/F$ unchanged       | CA             | Roy et al. (2010) [66]    |
|            |            |          | $AUC_{24}$ unchanged |                | NCA            | Verhagen et al. (2012) [78] |
|            |            |          | $AUC_{24}$ and $C_{max}$ decreased in stunting* |                | NCA            | Ramachandran et al. (2013) [77] |
|            |            |          | $AUC_{3}$ decreased* | Normalized $V_d/F$ unchanged | NCA            | Antwi et al. (2017) [55]   |
|            |            |          | $AUC_{3}$ and $C_{max}$ unchanged | Normalized $CL/F$ unchanged | NCA            | Ramachandran et al. (2016) [83] |
|            |            |          | $C_{2h}$ decreased* | Normalized $V_d/F$ unchanged | CA             | Rogers et al. (2016) [79]   |
|            |            |          | $C_{2h}$ and $K_m$ unchanged |                | NCA            | Ramachandran et al. (2017) [84] |
|            |            |          | $C_{2h}$ decreased* |                | NCA            | Dayal et al. (2018) [86]    |
|            |            |          | $C_{2h}$ decreased* |                | NCA            | Justine et al. (2020) [76]   |
|            |            |          | $AUC_{3}$ and $C_{max}$ decreased* | Plasma protein binding decreased* | NCA            | Polasa et al. (1984) [59]    |
|            |            |          | $T_{max}$ unchanged | $T_{max}$ increased         | NCA            | Garg et al. (1988) [65]   |
|            |            |          | $T_{max}$ increased  | $T_{max}$ and $k_c$ unchanged | NCA            | Seth et al. (1992) [18]   |
|            |            |          | $T_{max}$ decreased* |                | NCA            | Verhagen et al. (2012) [78] |
|            |            |          | $T_{max}$ increased  |                | NCA            | Ramachandran et al. (2013) [77] |
|            |            |          | $T_{max}$ decreased* |                | NCA            | Mukherjee et al. (2015) [90] |
|            |            |          | $T_{max}$ decreased* |                | NCA            | Ramachandran et al. (2016) [83] |
|            |            |          | $T_{max}$ decreased* |                | NCA            | Ramachandran et al. (2016) [83] |
|            |            |          | $T_{max}$ decreased* |                | NCA            | Ramachandran et al. (2016) [83] |
| Rifampicin |            |          | $AUC_{24}$ decreased* | $CL/F$ and $CL_R$ increased*; $T_{1/2}$ unchanged | NCA            | Polasa et al. (1984) [59]    |
|            |            |          | $AUC_{24}$ increased | $T_{1/2}$ increased         | NCA            | Garg et al. (1988) [65]   |
|            |            |          | $AUC_{24}$ increased | $T_{1/2}$ and $k_c$ unchanged | NA             | Seth et al. (1992) [18]   |
|            |            |          | $AUC_{24}$ decreased in stunting* and underweight* |                | NCA            | Verhagen et al. (2012) [78] |
|            |            |          | $AUC_{3}$ decreased* |                | NCA            | Ramachandran et al. (2013) [77] |
|            |            |          | $AUC_{3}$ and $C_{max}$ decreased* |                | NCA            | Mukherjee et al. (2015) [90] |
|            |            |          | $AUC_{3}$ and $C_{max}$ decreased* |                | NCA            | Antwi et al. (2017) [55]    |
|            |            |          | $AUC_{3}$ and $C_{max}$ decreased* |                | NCA            | Ramachandran et al. (2016) [83] |

△ Adis
### Table 5 (continued)

| Drug     | Absorption | Exposure | Distribution | Elimination | PK methodology | References                  |
|----------|------------|----------|--------------|-------------|----------------|-----------------------------|
| Pyrazinamide | $T_{\text{max}}$ unchanged | $C_{2h}$ unchanged | $C_{2h}$ unchanged | NCA | Ramachandran et al. (2017) [84] |
|          |            |          | $C_{2h}$ decreased* | NCA | Justine et al. (2020) [76] |
|          |            |          | AUC$_{24}$ and $C_{\text{max}}$ decreased; AUC$_{24}$/dose and $C_{\text{max}}$/dose unchanged | NCA | Graham et al. (2006) [88] |
|          |            |          | AUC$_{24}$ decreased | NCA | Verhagen et al. (2012) [78] |
|          |            |          | $C_{\text{max}}$ decreased in stunting* and underweight* | NCA | Ramachandran et al. (2013) [77] |
|          | $T_{\text{max}}$ changed* | $AUC_{24}$, $C_{2h}$, and $C_{\text{max}}$ unchanged | Normalized $V_d/F$ unchanged | Normalized $CL/F$ increased* | NCA | Antwi et al. (2017) [55] |
|          | $T_{\text{max}}$ decreased* | AUC$_{8}$ decreased*; $C_{\text{max}}$ unchanged | $C_{\text{max}}$ decreased in severe wasting*, stunting*, and severe malnutrition*; $C_{2h}$ decreased in severe malnutrition* | NCA | Ramachandran et al. (2016) [83] |
|          | $T_{\text{max}}$ changed | $C_{2h}$ unchanged | Normalized $V_d/F$ unchanged | Normalized $CL/F$ increased* | NCA | Antwi et al. (2017) [55] |
|          | $T_{\text{max}}$ unchanged | $AUC_{8}$, $C_{2h}$, and $C_{\text{max}}$ unchanged | Normalized $V_d/F$ unchanged | Normalized $CL/F$ increased* | NCA | Ramachandran et al. (2013) [77] |
| Ethambutol | $T_{\text{max}}$ changed | $AUC_{24}$, $C_{2h}$, and $C_{\text{max}}$ unchanged | $C_{\text{max}}$ decreased in underweight* | NCA | Mukherjee et al. (2015) [90] |
|          | $T_{\text{max}}$ unchanged | $AUC_{8}$, $C_{2h}$, and $C_{\text{max}}$ unchanged | Normalized $V_d/F$ unchanged | Normalized $CL/F$ increased* | NCA | Antwi et al. (2017) [55] |
|          | $T_{\text{max}}$ unchanged | $C_{2h}$ unchanged | $C_{2h}$ unchanged | NCA | Justine et al. (2020) [76] |
| Streptomycin | $T_{1/2,\text{abs}}$ unchanged | $V_d/F$ increased in kwashiorkor* | $V_d/F$ and plasma protein binding unchanged | $T_{1/2}$ unchanged | CA | Bolme et al., (1988) [54] |
|          | $T_{\text{max}}$ increased | Concentrations unchanged | $V_d/F$ and plasma protein binding unchanged | $T_{1/2}$ unchanged | CA | Bolme et al., (1988) [54] |
| Ofloxacin | $T_{\text{max}}$ unchanged | AUC$_{8}$, AUC$_{24}$, and $C_{\text{max}}$ unchanged | $V_d/F$ unchanged | $CL/F$ and $T_{1/2}$ unchanged | NCA | Garcia-Prats et al. (2015) [89] |
| Moxifloxacin | $T_{\text{max}}$ unchanged | AUC$_{3}$ decreased*; $C_{\text{max}}$ unchanged | $C_{\text{max}}$ unchanged | $C_{\text{max}}$ unchanged | NCA | Thee et al. (2015) [87] |
| Levofloxacin | $T_{\text{max}}$ unchanged | AUC$_{3}$ and $C_{\text{max}}$ unchanged | $C_{\text{max}}$ unchanged | $C_{\text{max}}$ unchanged | NCA | Kumar et al. (2018) [91] |
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 medications 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

| Drug          | Absorption | Exposure | Distribution | Elimination | PK methodology | References |
|---------------|------------|----------|--------------|-------------|----------------|------------|
| Ethionamide   | unchanged  | AUC<sub>4</sub> and C<sub>max</sub> | NCA | Kumar et al. (2018) [91] |
| Cyclosporine  | unchanged  | AUC<sub>4</sub> and C<sub>max</sub> | NCA | Kumar et al. (2018) [91] |

AUC area under the curve, AUC<sub>4</sub> AUC from time zero to 4 h, AUC<sub>8</sub> AUC from time zero to 8 h, AUC<sub>24</sub> AUC from time zero to 24 h, AUC<sub>∞</sub> AUC from time zero to infinity, C<sub>2h</sub> concentration at 2 h, CA compartmental analysis, CL/F apparent oral clearance, CL<sub>g</sub> renal clearance, C<sub>max</sub> peak concentration, f<sub>free</sub> unbound fraction, HAZ height-for-age Z-score, k<sub>E</sub> absorption rate constant, k<sub>el</sub> elimination rate constant, K<sub>m</sub> drug concentration where enzyme achieves half V<sub>max</sub>, NA not available, NCA noncompartmental analysis, PK pharmacokinetic, T<sub>1/2,abs</sub> absorption half-life, T<sub>1/2,el</sub> elimination half-life, T<sub>0</sub> terminal half-life, TB tuberculosis, T<sub>max</sub> time to maximum plasma concentration, V/F apparent volume of distribution, V<sub>max</sub> maximum enzyme binding rate, WAZ weight-for-age Z-score

*Significant difference
### 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; $T_{\frac{1}{2}}$ decreased | NCA | Gatti et al. (1999) |
| Stavudine  | $C_{\max}$ decreased* | NCA | | | NCA | Brantley et al. (2003) |
| Didanosine | $C_{\max}$ decreased | NCA | | | NCA | Brantley et al. (2003) |
| Lamivudine | $C_{\max}$ unchanged | NCA | | | NCA | Brantley et al. (2003) |
| Abacavir   | $k_a$ unchanged | $V_{d}/F$ unchanged | CL/F unchanged | CA | Archary et al. (2019) |
| 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) |
| Nevirapine | $C_{\max}$ increased in wasting*; $C_{\max}$ decreased in stunting* | AUC$_{12}$, $C_{\max}$, and $C_{\text{trough}}$ unchanged | NCA | Pollock et al. (2009) |
|            | $k_a$ unchanged | $V_{d}/F$ decreased with increasing TBW% | CL/F unchanged | CA | Vreeman et al. (2014) |
|            | $F$ increased* | $V_{d}/F$ decreased* | CL/F decreased* | CA | Bartelink et al. (2015) |
| Lopinavir  | $F$ unchanged | CL/F unchanged | CA | Bartelink et al. (2014) |
|            | $F$ decreased* | $V_{d}/F$ increased* | CL/F increased* | CA | Bartelink et al. (2015) |
| Efavirenz  | $F$ unchanged | CL/F unchanged | CA | Bartelink et al. (2014) |
|            | $F$ decreased* | $V_{d}/F$ increased* | CL/F increased* | CA | Bartelink et al. (2015) |
| Ritonavir  | $F$ unchanged | CL/F unchanged | CA | Bartelink et al. (2014) |
| Zidovudine | $C_{\max}$ unchanged | NCA | CL/F decreased in wasting*; $T_{\frac{1}{2}}$ unchanged | NCA | Filleke et al. (2014) |
|            | AUC$_{12}$ increased in wasting*, $C_{\max}$ and $C_{12h}$ unchanged | NCA | | | |

$AUC$ 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, $C_{\text{trough}}$ 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, $T_{\frac{1}{2}}$ terminal half-life, TBW% total body water percentage, $T_{lag}$ absorption lag time, $T_{\max}$ time to reach $C_{\max}$, $V_{d}/F$ central volume of distribution, $V_{d}/F$ volume of distribution, $V_{p}/F$ peripheral volume of distribution

*Significant difference
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

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**Table 7 Pharmacokinetic results of malaria studies**

| Drug       | Absorption | Exposure | Distribution | Metabolism | Elimination | PK methodology | References                |
|------------|------------|----------|--------------|------------|-------------|----------------|--------------------------|
| Chloroquine|            |          |              | Drug/metabolite ratio increased* | CL/F increased*; $T_{1/2}$ increased | NCA | Wharton and McChesney (1970) [69] |
|            | AUC unchanged |        |              |            |             |                |                          |
|            | AUC decreased* |     |              | Drug/metabolite ratio increased | $T_{1/2}$ unchanged | NCA | Tulpule and Krishnaswamy (1983) [74] |
|            | $T_{max}$ increased |  | AUC$_{168}$, AUC$_{ao}$, and $C_{max}$ unchanged | CL/F unchanged; $T_{1/2}$ unchanged | NCA | Walker et al. (1987) [70] |
|            | $T_{max}$ increased |  | AUC$_{ao}$ increased; $C_{max}$ unchanged | Drug/metabolite ratio unchanged; $T_{1/2}$ unchanged | NCA | Dua et al. (2002) [71] |
|            | $T_{max}$ increased |  | $V_d/F$ decreased | Drug/metabolite ratio unchanged | NCA | Kadam et al. (2016) [52] |
| Quinine    | $T_{1/abs}$ increased* |  |              |            |             |                |                          |
|            | AUC increased*; $C_{max}$ decreased* |  |              | CL/F decreased*; $T_{1/2}$ increased | CA | Salako et al. (1989) [72] |
|            | $T_{max}$ decreased* |  | $C_{max}$ unchanged; $C_{12h}$ decreased | $V_d/F$ and plasma protein binding unchanged | NCA | Treluyer et al. (1996) [26] |
|            | $T_{max}$ decreased* |  | AUC$_{ao}$ and $C_{max}$ increased* | Drug/metabolite ratio decreased* | NCA | Pussard et al. (1999) [58] |
| Lumefantrine|            |        |              |            |             |                |                          |
|            | $C_a$ decreased in children < 3 years of age |  |              | CL/F increased*; $T_{1/2}$ increased | NCA | WWARN (2015) [93] |
|            | $F$ decreased* |  |              | CL/F decreased*; $T_{1/2}$ increased | CA | Chotsiri et al. (2019) [47] |
| Sulfadoxine| $F$ decreased* |  |              |            |             |                |                          |
|            | $F$ decreased* |  |              |            |             |                |                          |
| Pyrimethamine|            |        |              |            |             |                |                          |

*AUC area under the curve, AUC$_{ao}$ AUC from time zero to 8 h, AUC$_{168}$ AUC from time zero to 168 h, AUC$_{ao}$ 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, $T_{1/abs}$ apparent absorption half-life, $T_{1/2}$ terminal half-life, $T_{max}$ time to reach $C_{max}$, $V_d/F$ volume of distribution

*Significant difference
*Day 7 concentrations at different time points
Pharmacokinetics in Malnutrition and Poverty-Related Diseases 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 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.

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.
although evidence was not sufficiently strong to establish
dosing recommendations [85]. These studies suggested a
clinically relevant impact of malnutrition on the pharma-
cokinetics of certain PRD drugs. Various studies included in
this systematic review addressed the need for dose adjust-
ments 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 malnour-
ished 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 moder-
ately 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 poten-
tially 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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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 par-
ticipated in the interpretation of the study results and in the drafting,
critical revision and approval of the final version of the manuscript.

Availability of data, material and code Not applicable.

Ethical approval and consent to participate Not applicable.

Consent for publication Not applicable.

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